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THE HEART IN HYPERTHYROIDISM:* EFFECT OF ANTITHYROID DRUGS AND I^{131}

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Thyrotoxicosis imposes a severe strain on the cardiovascular system, which expresses itself in the clinical picture commonly referred to as thyroid heart disease. This is diagnosed when atrial fibrillation and congestive heart failure are present in the hyperthyroid patient.

Many authors (1) feel that this occurs only in patients who have some preexisting disorder of the heart such as hypertensive, valvular, or coronary arteriosclerotic heart disease, and express doubt as to the existence of thyroid heart disease per se. Other authors (2), after studying large series of thyrotoxic patients, conclude that hyperthyroidism alone can account for this picture.

In the past several years we have had the opportunity to study several of these patients clinically, and 1 of them at autopsy. We have also studied the effect of antithyroid drugs. As a result of these observations we believe that the hyperthyroid state in itself can be the cause of this cardiac condition.

CASE REPORTS

The following case reports exemplify problems of cardiac function complicating the hyperthyroid state:

Case 1

Mrs. R. H., aged 40. This patient was seen in September 1953 for the complaint of swollen legs and ankles, of nine months' duration.

She had been well until the age of 31 when, after a protracted nervous strain, thyrotoxic symptoms and marked weight loss developed. Following treatment with propylthiouracil, a subtotal thyroidectomy was performed in 1947. After a brief relief of symptoms she suffered a recurrence of thyrotoxicosis accompanied by enlargement of the goiter. A second operation was followed by relief of symptoms in 1949; postoperatively she was given local radiation and Lugol's solution. Her condition was fairly satisfactory until June 1953, when congestive heart failure developed. In addition she ceased menstruating.

When seen in September 1953, her weight was 175 pounds, and blood pressure 145/90. She was acutely dyspneic. The characteristic eye signs and a coarse tremor were present.

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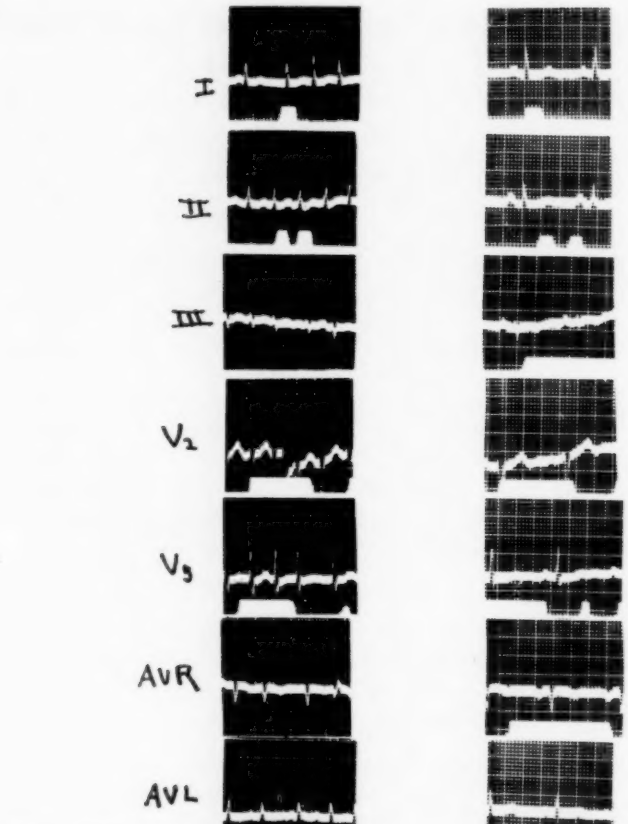

FIG. 1. Electrocardiogram in Case 1, showing atrial fibrillation with return to sinus rhythm eight weeks later.

Both lobes of the thyroid were enlarged and estimated to weigh 40 Gm. each. Examination of the heart revealed enlargement to the left, an apical rate of 200 beats per minute, atrial fibrillation and a marked pulse deficit. There was bilateral pleural effusion and hepatic enlargement. Pitting edema extended upward to the mid-chest. Fluoroscopic and radiographic examination of the chest confirmed the cardiac enlargement and pulmonary findings. The electrocardiogram confirmed the atrial fibrillation and ventricular rate of 200 beats per minute (Fig. 1).

The day after hospitalization the basal metabolic rate (BMR) was +85 per cent. The venous pressure was 270 mm. of water, and the circulation time prolonged. She was given 0.45 Gm. of whole-leaf digitalis daily during the hospital stay, and also thiamine chloride, mercurial diuretics and a daily dose of 30 mg. of 1-methyl-2-mercaptoimidazole (methimazole, Tapazole).

During the twenty days of hospitalization compensation gradually took place and the patient lost about 30 pounds. After discharge she was kept in bed at home for an addi-

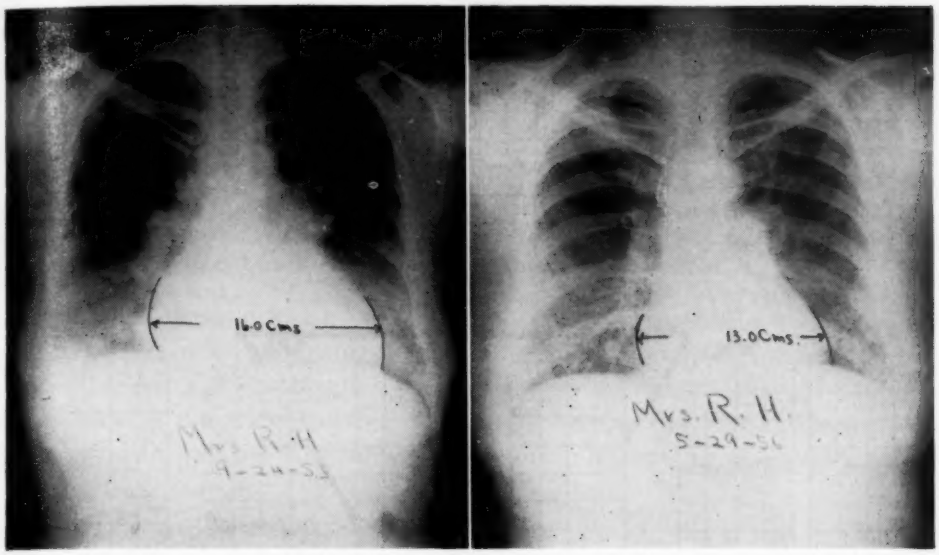

FIG. 2. Roentgenogram of chest before treatment and thirty-two months later after heart was fully compensated.

tional four weeks. During this time she was maintained on 0.3 Gm. of digitalis. Cardiac compensation improved and spontaneous reversal to sinus rhythm was noted.

Seven weeks after beginning methimazole, the BMR was +23 per cent and thyroidal I^{131} uptake was estimated at 90 per cent. At this time a dose of 8 millicuries of I^{131} was given and twelve weeks later, when the uptake was found to be 60 per cent, an additional 5.5-millicurie dose was given. Three months later the uptake was 48 per cent. A final dose of 4.3 millicuries was given, making the total dosage 16.5 millicuries. After eleven months of treatment, digitalis was omitted. There was excellent compensation and the patient was in a euthyroid state. The BMR was +7 per cent and the serum protein-bound iodine level was 6.1 micrograms per 100 cc. The electrocardiogram was normal and the heart size, as determined radiographically, was within normal limits (Fig. 2). Menstruation occurred regularly and she was able to carry on normal housework and care for a family of five.

Comment. A full year was required for restoration of normal cardiac activity and a euthyroid state. This represents thyrotoxic heart disease in a person with no previous history of heart disease or any demonstrable lesion at present.

Case 2

Wm. C., aged 47, entered the Saint Louis City Hospital on August 18, 1952. He had been perfectly well until ten months prior to entry, when he noted progressive weakness, nervousness, tremor and diarrhea. In spite of an increased appetite he lost over 90 pounds. A brief episode of congestive failure had been improved by administration of thiouracil and digitalis by his private physician. Two weeks before entry there was a recurrence and he was in a state of acute cardiac failure when admitted.

On examination the blood pressure was 140/60; respiration, 35 per minute; and pulse, 136 (irregular). There was marked dyspnea, advanced generalized edema and bilateral exophthalmos. The thyroid gland was diffusely enlarged and there was a small nodule in the right lobe. The heart was enlarged to the left, the rate was rapid, and atrial fibrillation was noted. There were rales in the lungs bilaterally and evidence of fluid on the right. The liver was enlarged 4 cm. below the right costal margin and there was free fluid in the

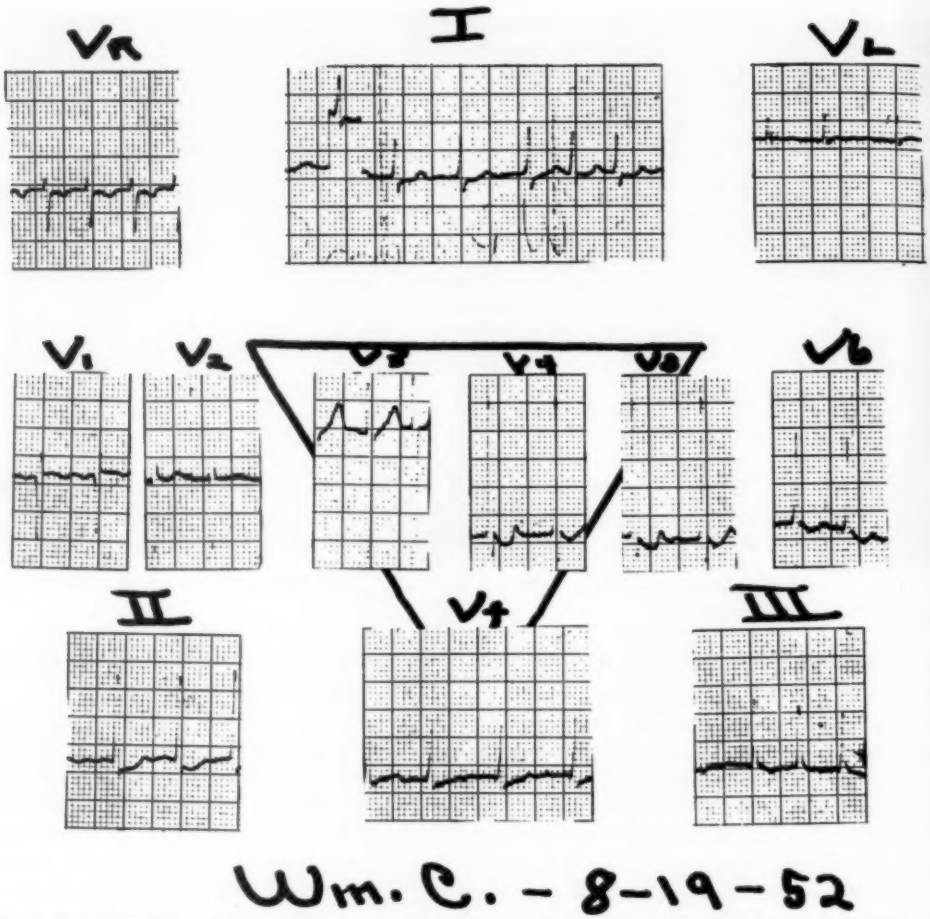

FIG. 3. Initial electrocardiogram in Case 2, showing atrial fibrillation and myocardial changes.

abdominal cavity. Edema extended as high as the mid-epigastrium. The venous pressure was elevated to 285 mm. of water, and the circulation times were prolonged. The BMR was +65 per cent and thyroidal I^{131} uptake was 87 per cent. X-ray examination of the chest showed cardiac enlargement, congestion of the bases, and right hydrothorax. The electrocardiogram (Fig. 3) showed atrial fibrillation, ventricular extrasystoles and myocardial changes. Results of laboratory studies, including blood count, urinalysis, and electrolyte determinations were normal.

Treatment consisted of absolute bed rest, 0.1 Gm. of whole-leaf digitalis daily, thiamine chloride, mercurial diuretics and 30 mg. of methimazole daily.

After six weeks the heart was well compensated. The BMR was +48 per cent. The patient was given 6 millicuries of I^{131}. Seven weeks after entry he was discharged to the clinic, maintained on digitalis and methimazole. There he was followed for a three-month period; the heart remained well compensated, although atrial fibrillation persisted. He was not seen again for seven months, at which time thyroidal I^{131} uptake was 90 per cent. Due to his demonstrated failure to cooperate, it was decided to give him another trial of I^{131}, so a dose of 16 millicuries was given. He did not report back to the clinic for over two years, during which time his condition was fairly satisfactory.

In January 1956 symptoms and signs of congestive failure again developed, and in April 1956 he finally reported to the clinic. He was thyrotoxic and had marked cardiac decom-

pensation. On examination after immediate hospitalization the heart was found to be fibrillating at a rate of 150 beats per minute. The thyroid gland was enlarged and nodular. Congestive failure was severe and the venous pressure measured 340 mm. of water. The BMR was +50 per cent and thyroidal I^{131} uptake was 85 per cent. The serum protein-bound iodine level was 10 micrograms per 100 cc. The blood count and electrolyte determinations were normal. The serum cholesterol level was 136 mg. per 100 cc.

On May 8, 1956, a dose of 10 millicuries of I^{131} was given, and methimazole was started in a dosage of 30 mg. daily. Measures for the control of congestive failure, including digitalization, were again instituted. Within a few weeks the patient was discharged to the clinic free of signs of congestive failure. Atrial fibrillation persisted, however.

Comment. This man was a very difficult person to treat. He would not cooperate in an extended program, so it was deemed imperative to treat him with radioactive iodine, even though a preliminary period of methimazole would have been advantageous. This proves the need to stress the long-range aspects of therapy and the necessity of careful follow-up to maintain a euthyroid state and normal cardiac function.

Case 3

Mrs. C. H., aged 47, was first seen by us in 1945. She had had a goiter for ten years, without thyrotoxicosis. The thyroid was diffusely enlarged; the pulse rate, 78 beats per minute; and blood pressure, 130/78. Thorough examination of the heart failed to reveal any abnormality. BMR's were −11 per cent and −14 per cent. In 1948, after the death of a parent, marked nervousness, tremor, weight loss in spite of increased appetite, and other symptoms of hyperthyroidism developed. The BMR was found to be +34 per cent; and the pulse 132 beats per minute, with sinus rhythm. The cardiovascular evaluation otherwise was normal.

A euthyroid state was attained in fifteen weeks with the use of propylthiouracil (300–400 mg. per day). During the next eight months she was well maintained on this drug and uneventfully underwent two major operations—complete hysterectomy and right nephrectomy. During this time there was no sign of atrial fibrillation or cardiac failure. Propylthiouracil was continued for the next year, and her condition was satisfactory. The BMR was +15 per cent in 1949. During the next year she became rather indifferent to treatment.

When next seen in November 1950 she had lost weight, was quite nervous, and the thyroid gland was enlarged. The BMR was +35 per cent. The electrocardiographic tracing indicated a normal heart except for sinus tachycardia of 108 beats per minute (Fig. 4). Thyroidal I^{131} uptake was in the hyperthyroid range, and on December 19, 1950, she was given 6 millicuries of I^{131}. For the next ten weeks she did poorly, and by March 6, 1951, had lost an additional 8 pounds. The BMR had risen to +57 per cent, and the heart rate was rapid. Signs of congestive failure or cardiac enlargement were lacking at this time.

One month later she had gained 17 pounds, and demonstrated atrial fibrillation, cardiomegaly, and moderately advanced congestive failure. She was hospitalized, and soon a thyroid crisis occurred. In spite of intravenous iodine and glucose, oxygen, digitalis, and other support she went rapidly downhill. Paroxysmal auricular tachycardia developed, for which quinidine proved ineffective. She died within a few days.

Postmortem examination showed congestion in both lungs and free fluid in the pleural spaces. The pericardial sac contained a small amount of fluid. The heart was enlarged and weighed 450 Gm. The pericardial surface was normal. The right ventricular wall measured 0.4 cm. in thickness and the left ventricular wall 1.8 cm. The coronary arteries were carefully dissected and no evidence of narrowing or atheromata was found. The valves were all thin and showed no abnormality. As seen in Figure 5, the muscle fibers were generally normal, but there were many areas of degeneration and disruption of the normal pattern.

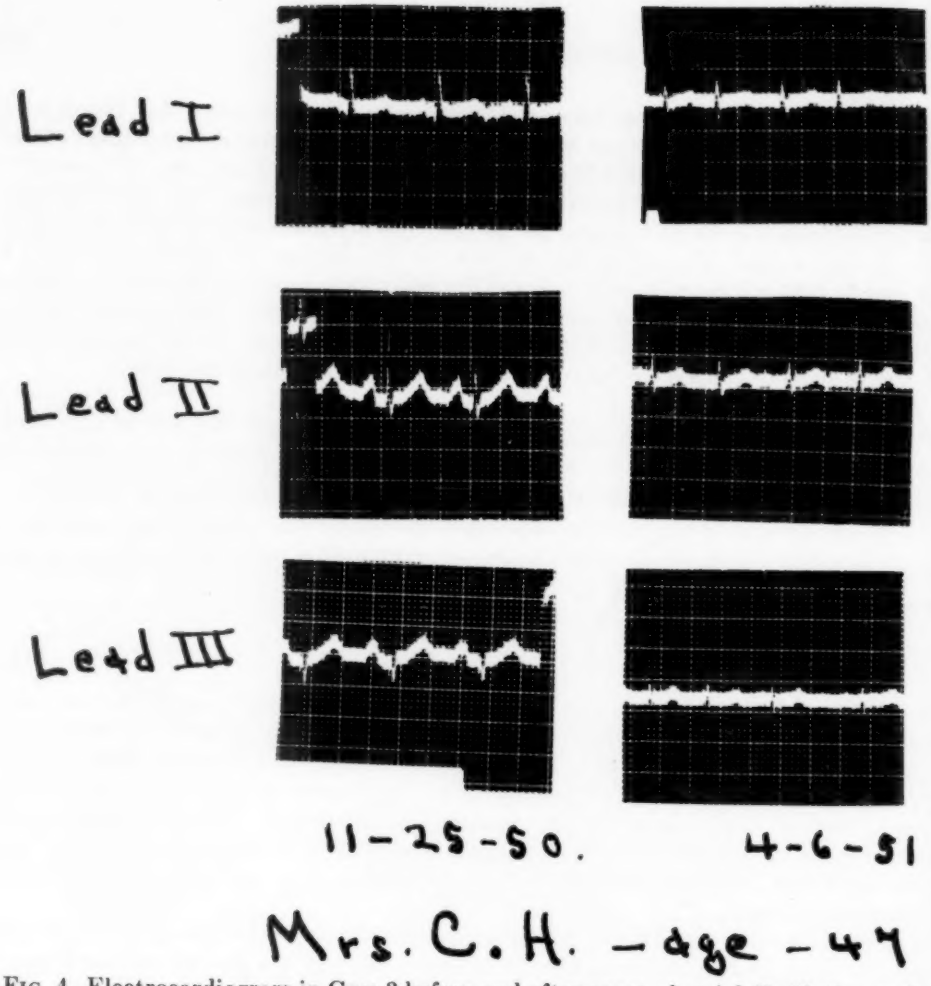

FIG. 4. Electrocardiogram in Case 3 before and after onset of atrial fibrillation and congestive failure.

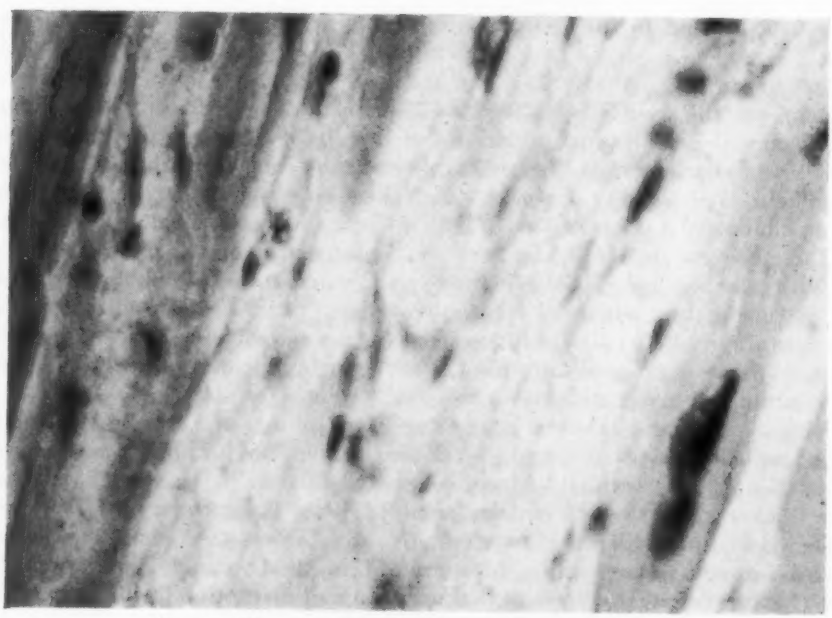

FIG. 5. Showing changes in cardiac muscle fiber

Very little round-cell infiltration was noted. There were occasional areas of focal fibrosis. The liver was enlarged, weighed 1280 Gm., and had the nutmeg appearance of chronic passive congestion.

Comment. This patient had Graves's disease of long standing, with previously induced remissions from iodine and propylthiouracil. She had satisfactorily withstood two major surgical procedures under this suppressive therapy. The cardiovascular manifestations occurred in the last three months of life, after a long period of inadequate treatment evoked by poor cooperation on her part. Because of the failure to cooperate in the past, it was felt that radioiodine therapy was advisable. At this time there were no reports in the literature of thyroid storm following the use of I^{131}, but a review of this case suggests that sequence of events. Following this experience, and in view of the report of Skillern (3) and associates, we have adopted a pre-I^{131} period in the treatment of patients with hyperthyroidism and advanced cardiac involvement. An antithyroid drug is administered until a euthyroid state is approached, following which radioactive iodine is administered.

SUMMARY

Although there is a difference of opinion as to whether or not the hyperthyroid state causes a specific type of heart lesion, there is little doubt that disturbance of rhythm, cardiac failure, and alterations in cardiac size can occur as a direct result of this disease. Atrial fibrillation occurs in 90 per cent of all hyperthyroid patients with cardiac failure (4).

Correction of the hyperthyroid state in younger patients is followed by normal sinus rhythm and cardiac compensation. This is not as true in older patients in whom coronary sclerosis is presumably present and considered to be an added factor in the causation of the cardiac disorder. Cardiomegaly that results from the hyperthyroid state is not always completely reversible, although there may be no apparent cause for it other than the thyrotoxicosis. Changes in the heart muscle have been demonstrated microscopically in a patient who died in a thyroid crisis. It is felt that these changes were directly attributable to the long standing thyrotoxicosis. Deficiency of thiamine chloride (5, 6) occurs in the hyperthyroid state due to its rapid utilization by the body, and may be a factor in the changes noted, although an effort was made to keep the intake of this vitamin at a high level in all patients studied.

The need for a long-term therapeutic program in these cases is evident. Surgical procedures should be carried out only after the patient's hyperthyroid state is well controlled by an antithyroid drug and the cardiac status is considered satisfactory.

The course of events in the patient who died in a thyroid crisis following administration of I^{131} suggests that an increase in circulating thyroxine follows a therapeutic dose of this isotope. It is therefore our practice to treat all cases of thyrotoxicosis, (whether or not there is associated cardiac failure) with an antithyroid drug until the disease is reasonably well controlled. This may require from ten to twenty weeks, during which time cardiac compensation may be effected by restricted activity, administration of digitalis and diuretics, and other

supportive measures. Then I^{131} can be administered without fear of activation of symptoms.

The diagnosis of hyperthyroidism must be excluded in all cases of unexplained atrial fibrillation or cardiac failure.

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MANAGEMENT OF CHRONIC ADRENOCORTICAL INSUFFICIENCY WITH ORAL REPLACEMENT THERAPY*

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With the ready availability of adrenal steroids which are primarily glucocorticoid in physiologic activity and the recent development of their halogenated steroid analogs (1, 2), the effective therapeutic control of adrenocortical insufficiency has been greatly simplified and the need for parenteral replacement therapy has been obviated. In most patients, oral therapy with cortisone or hydrocortisone alone adequately controls disturbances in carbohydrate metabolism, but lack of mineralocorticoid activity may result in incomplete electrolyte regulation, manifested by hyponatremia, hypotension, nausea, diarrhea, and continued weakness without periodic attacks of syncope.

In patients with adrenocortical hypofunction (Addison's disease), therapeusis of the deficiency of electrolyte-regulating hormone has ranged from 1) the erratic control with large doses of sodium chloride by mouth, 2) intermittent control with frequent and massive doses of aqueous adrenal cortical extract, 3) regulation with parenteral administration of desoxycorticosterone derivatives, to 4) simple, but effective management with oral dosage of fludrocortisone acetate (9-alpha-fluoro-hydrocortisone) (Table 1). An advance in therapeutics over the necessity of frequent intramuscular injection of maintenance doses of desoxycorticosterone acetate in oil was achieved by pellet implantation of the same steroid, resulting in effective control of the disease for an average of eight to twelve months. More recently, Thorn and his co-workers recommended intramuscular administration of an aqueous suspension of desoxycorticosterone trimethylacetate which, by virtue of its slow absorption, need be given only once every thirty days to most patients (3). Attempts to overcome the need for parenteral administration of the mineralocorticoid-regulating factor led to the use of desoxycorticosterone acetate in lingual form (4); when given in adequate dosage in conjunction with oral cortisone, this resulted in satisfactory control in some cases of Addison's disease. However, the sublingual route may cause faulty or irregular absorption by virtue of the fact that most of the steroid may be washed down to the stomach by salivary secretion. Partial inactivation of the steroid by the liver in these patients then yields variable and unpredictable therapeutic results.

Recent studies on the biologic activity of 9-alpha-fluorohydrocortisone and related halogenated steroids in man and animals have demonstrated the predominant sodium-retaining effects of these compounds when administered orally

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TABLE 1

Evolution of Mineralocorticoid Replacement Maintenance Therapy in Hypoadrenocorticoidism

Therapy	Route	Average Dose		
		Amount	Frequency	Duration of effect
Salt	Oral	3–4 Gm.	Three times daily	6 hrs.
Adrenal cortical extract	Intramuscular or subcutaneous	10–20 cc.	Daily	24 hrs.
Desoxycorticosterone acetate	Intramuscular;	2.5 mg.	Daily	24 hrs.
	pellet implantation;	250 mg.	Every 8–12 mos.	8–12 mos.
	lingual	2–4 mg.	Variable	Variable
Desoxycorticosterone trimethylacetate	Intramuscular	37.5 mg.	Every 30 days	5–6 wks.
Fludrocortisone acetate	Oral	0.1 mg.	Daily	24 hrs.

(5, 6) or applied topically (7). In the doses employed, their influence on carbohydrate metabolism is overshadowed by their effect upon electrolyte metabolism. We studied fludrocortisone acetate in patients with the adrenogenital syndrome, comparing its adrenocorticotropic-inhibiting properties to those of other corticoid steroids. Not only was there effective inhibition of endogenous corticotropin secretion when fludrocortisone was used in doses of 2 to 3 mg. per day, but there was also the undesirable effect of profound sodium retention with edema (8). This latter phenomenon led us to the evaluation of the use of this drug as an adjunct to hydrocortisone in the complete oral replacement therapy of patients with primary or secondary hypofunction of the adrenal cortex (9, 10).

CLINICAL DATA

Eight patients with chronic adrenal insufficiency were observed for periods of from six to twenty months while receiving daily oral doses of fludrocortisone acetate and hydrocortisone (Table 2).[1] Five of this group had primary adrenocortical hypofunction—due to idiopathic adrenocortical failure in 4, and due to total adrenalectomy for adrenocortical hyperfunction (Cushing's syndrome) in 1. The remaining 3 patients had adrenocortical insufficiency secondary to pituitary failure—following irradiation therapy to the pituitary for acromegaly in 1, following postpartum pituitary necrosis (Sheehan's syndrome) in 1, and secondary to a suprasella neoplasm in 1. All but 1 of the patients were maintained on hydrocortisone (10 mg. twice daily) and fludrocortisone acetate (0.25 mg. every other day, or 0.1 mg. daily). This exceptional case will be discussed. The patients were given a free diet with no sodium restrictions or supplementations. Therapeutic control was accomplished with ease and was well maintained, as manifested by the patients' abilities to perform a full day's activities with no subjective symp-

[1] The 9-alpha-fluorohydrocortisone and hydrocortisone used in this study were supplied through the courtesy of Dr. Gilbert Bayne of Sharpe and Dohme.

TABLE 2

Primary or Secondary Hypoadrenocorticoidism Treated with Fludrocortisone Acetate and Hydrocortisone

Case No.	Age (yrs.)	Sex	Diagnosis	Duration of Treatment with FA and H (mos.)	Previous Therapy with Other Adrenal Steroids
1	29	F	Secondary adrenocortical hypofunction (suprasellar neoplasm)	13	None.
2	45	F	Primary adrenocortical hypofunction	19	Desoxycorticosterone trimethylacetate, 50 mg. every mo.; cortisone, 20 mg. every day.
3	60	M	Secondary adrenocortical hypofunction; pituitary irradiation	13	Desoxycorticosterone trimethylacetate, 25 to 37.5 mg. every mo.
4	50	M	Primary adrenocortical hypofunction	12	Desoxycorticosterone acetate, 2.5 mg. every day.
5	29	F	Adrenalectomy for adrenocortical hyperfunction (Cushing's syndrome)	20	Cortisone, 12.5 mg. twice daily.
6	39	M	Primary adrenocortical hypofunction	18	Desoxycorticosterone trimethylacetate, 50 mg. every 4 to 5 wks.; cortisone, 10 mg. twice daily.
7	32	F	Secondary adrenocortical hypofunction (Sheehan's syndrome)	6	None.
8*	73	F	Primary adrenocortical hypofunction	9	None.

* Fludrocortisone acetate discontinued after five months because of recurrence of diastolic hypertension.

toms of weakness, fatigue, or anorexia. The previous maintenance therapy is outlined in Table 2.

In Case 8 (Table 2) the patient was a 73-year-old Negress whose therapy differed somewhat from that of the rest of the patients in this series. She had a previous history of hypertension of five to ten years' duration, with blood pressures repeatedly in the range of 200/120–130 mm. Hg. For two years prior to the diagnosis of idiopathic primary adrenocortical hypofunction she had symptoms of weakness, dizziness, muscle cramps, nausea and vomiting, and when seen in September 1955 had a blood pressure of 70/30–40 mm. Hg. A diagnosis of Addison's disease was made on the basis of a 24-hour 17-ketosteroid excretion of 3.4 mg., and lack of a 17-ketosteroid or eosinophil response to an intravenous corticotropin (ACTH) test.

While in the hospital during her initial period of observation, the patient suffered an adrenal crisis with severe hypotension, weakness and vomiting. Injection of 100 mg. of free hydrocortisone intravenously and 5 mg. of desoxycorticosterone acetate intramuscularly induced a dramatic response associated with complete recovery from the crisis. For the following month her condition was well controlled with 0.25 mg. of fludrocortisone

acetate and 20 mg. of hydrocortisone daily by mouth. Her blood pressure was 120/80. Subsequently, the dosage of halogenated steroid was decreased to 0.25 mg. every other day. She was well, her weight was stable, and she had returned to work.

Five months after the onset of treatment an increase in blood pressure from 110/75 to 160/96 was noted in a three-week period and she also complained of frequent headaches. Therefore, the fludrocortisone was discontinued. One week later, blood pressure returned to 110/76 and has remained at that level for the past four months during treatment with hydrocortisone alone.

The recurrence of hypertension in a patient such as this, even though she was receiving such small doses of fludrocortisone, illustrates the need for following the progress of the patient during treatment, and also the great flexibility of the control that can be achieved with this oral therapy. Had this patient received one of the long-acting parenteral preparations of desoxycorticosterone, there would have been little the physician could do to avoid a prolonged hypertensive phase other than await the eventual dissipation of the drug. The hypertensive episode also demonstrates the unusual paradox of the marked sensitivity that the Addisonian patient exhibits to sodium-retaining corticoids. Comparable doses in the normal individual would not appreciably affect the blood pressure.

DISCUSSION

To arrive at a correct maintenance dose of fludrocortisone for any patient, the physician must use its electrolyte-regulating properties to control symptoms of adrenal insufficiency, while avoiding the manifestations of excessive sodium retention. Criteria of overdosage with fludrocortisone are readily established by the following three simple clinical guides: 1) weight gain, 2) presence of edema, and 3) elevation in blood pressure. A fourth manifestation, easily detected by fluoroscopy, is a sudden excessive increase in the size of the heart. With such criteria, the dose may be readily reduced and later adjusted to the level required for adequate correction of any deviation from normal. The "toxic" manifestations of this mineralocorticoid are dissipated within a week merely by discontinuing treatment for three to five days. Treatment with the drug may be re-instituted at a lower dosage level. In 7 of the 8 patients in this series the adrenocortical insufficiency was well controlled with fludrocortisone in a dosage of 0.25 mg. every other day or 0.1 mg. daily.

The effectiveness of combined oral fludrocortisone-hydrocortisone therapy in correcting chronic adrenocortical insufficiency has been demonstrated by the repeated observation of recurrence of symptoms within seven to fourteen days after discontinuing the maintenance dose of fludrocortisone acetate. Reversal of such induced adrenocortical hypofunction is accomplished by re-instituting therapy with larger oral doses of fludrocortisone in the range of 0.5 to 1.0 mg. per day, for two to four days.

It is of interest that in 2 patients a decrease in the hyperpigmentation associated with primary adrenocortical hypofunction was observed while they were being treated with fludrocortisone combined with hydrocortisone. This decrease in pigmentation may be ascribed to the inhibitory effect that the halogenated and free corticoid has upon the excessive pituitary secretion of corticotropin usually noted in patients with primary hypoadrenocorticoidism.

SUMMARY

Fludrocortisone acetate (9-alpha-fluorohydrocortisone) is an effective mineralocorticoid in the management of patients with chronic adrenocortical hypofunction. When administered in the recommended dosages, together with hydrocortisone, complete oral replacement therapy is achieved, and both electrolyte and carbohydrate disturbances are corrected. This combined oral therapy provides for the convenient therapeutic management of adrenal insufficiency, usually without manifestations of inadequate treatment or of overdosage.

The efficacy of this combination of drugs was observed over periods of six to twenty months in 8 patients. There were no signs of hypernatremia when the recommended doses were employed, except in 1 patient with typical Addisonian hypotension who had a history of previous hypertension. Both the pain and the inconvenience of parenteral therapy were obviated, and the patients were maintained in a steady state of control without noticeable alterations or symptoms of fatigability or muscular weakness. If overdosage with fludrocortisone occurred (as characterized by increased weight gain, edema, headaches and hypertension), it was readily resolved by discontinuing the fludrocortisone for from three to five days.

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TRENDS IN DRUG THERAPY*

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Trends in drug therapy are reflected at any given time by the type and variety of therapeutic agents recently developed for clinical use. They are mirrored also by newly found applications or unexpected hazards encountered in the use of older drugs. To the extent that new drugs and new knowledge of older drugs represent advances in therapy, or embody a new approach to clinical problems, they are likely to influence therapeutics. The interplay of influence between the new and the old ultimately shapes the relative importance of additions to the therapeutic armamentarium. Since I do not have a crystal ball by which to judge the future, it seems best to limit this presentation to a brief review of recent developments from which you may judge the degree to which they are indicative of trends in this important field.

In any survey of this kind one is impressed by both the number and variety of recently introduced drugs as well as the diversity of clinical conditions for which they are proposed. Although, in general, new advances are apt to follow the pattern of prior discoveries and further investigations are likely to proceed most intensively in the areas where new drugs are sorely needed, modern methods for screening large numbers of potential new therapeutic agents, have greatly expanded the capacity for developing new compounds. In today's rapidly expanding field of therapeutics, it is virtually impossible to cover all of the areas in which improvements have been made or are being sought. Some of the minor additions to drug therapy can be viewed as the result of competitive effort on the part of industry which tends to stimulate the introduction of numerous similar-acting compounds. Such variants often exhibit slightly different, though not necessarily improved properties. Others, which are more distinctive, can be expected to exert a greater impact on therapeutics. In the brief time allotted, it seems best to confine this subject to the principal areas in which investigation appears to offer some promise of future advances. Some of the compounds mentioned are not available except for investigational use, and no attempt is made to document all sources of information.

AGENTS USED IN ALLERGY

In allergy, additional antihistamine compounds continue to make their appearance, but the chief item of interest in this area arises from the use of injectable older compounds for the prevention and treatment of non-hemolytic, nonpyrogenic transfusion reactions (1). Developments concerning the use of anti-

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histamines for purposes other than allergy will be mentioned briefly in conjunction with hypnotics and sedatives.

ANTI-INFECTIVES

The search for new anti-infective agents continues unabated despited previous advances which have been made in the control of bacterial infections. The antifungal antibiotic, nystatin (Mycostatin) represents the first of this type of agent capable of controlling localized monilial infections due to C. albicans (2). One of the most interesting of the recently developed anti-infectives is the compound, cycloserine (Oxamycin, Seromycin), which has little *in vitro* action against Mycobacteria but exhibits clinical activity against pulmonary tuberculous infection as well as other bacteria (3). Its future usefulness in tuberculosis may reside chiefly in its concomitant administration with other antituberculosis agents and, because of the ease with which high concentrations of the drug are achieved in the body fluids, also in its use alone for the treatment of urinary-tract infections (4). New derivatives of isoniazid which exhibit less toxicity in mice are undergoing further clinical investigation for possible use in tuberculosis. Novobiocin (Albamycin, Cathomycin), a recently developed antibiotic also designated streptonivicin and cardelmycin (5), has a broader spectrum than penicillin and is more active against staphylococci. In addition to staphyloccal and other gram-positive infections, it is active also against certain gram-negative bacilli. A new derivative of penicillin, phenoxymethyl penicillin (Pen-Vee, V-Cillin) also known as penicillin V, appears to be as effective orally as penicillin G, but more resistant to inactivation by gastric juice (6). New antibiotics continue to be isolated in the laboratory, but their clinical usefulness is frequently limited by toxicity. Sorely needed, but not in prospect, are more effective agents to combat infections due to the naturally resistant species of bacteria such as pyocyaneus and proteus, and those due to the small viruses. An antiviral chemotherapeutic agent, caprochlorone, found active in the laboratory against influenza virus is a synthetically derived disubstituted oxohexanoic acid. The fact that these synthetic compounds exhibit antiviral activity offers some promise that such infections eventually may be controlled by chemotherapy. Piperazine salts, effective against both pin worms and round worms, apparently have displaced some of the older, more toxic anthelmintics previously employed to eradicate such parasites. Still other new compounds are under study for helminthic infections as well as for protozoal infections such as trypanosomiasis and leishmaniasis.

CARDIOVASCULAR AGENTS

In the area of cardiovascular drugs the problem of atherosclerosis in coronary disease, the use of vasopressors to control hypotensive shock accompanying myocardial infarction, and the development of potent hypotensive agents for the management of severe hypertension are attracting major attention. Oral administration of a soya extract of sitosterols (Cytellin) to increase the excretion of cholesterol and combat hypercholesterolemia is proposed for adjunctive use

in controlling the intake of dietary fat as another means of discouraging the progression of atherosclerosis (7). The cerebroside fraction of a mammalian brain extract also has been found to be active orally in reducing the serum cholesterol level in patients with coronary disease. The effectiveness of such agents in arresting the progression of atherosclerosis has not been definitely established. The vasopressor agents, levarterenol (Levophed) and mephentermine (Wyamine) which have a positive inotropic action on the heart, and methoxamine (Vasoxyl) which does not, are proposed for early use in the treatment of shock accompanying myocardial infarction. Their administration requires caution in order to avoid excessive elevation of blood pressure. Further interest has been reawakened in the use of digitalis as a cardiotonic in myocardial infarction, but this would appear to require additional careful studies. Routine use versus selection of patients for anticoagulant therapy of coronary thrombosis continues to undergo further evaluation. The use of drugs in hypertension reveals an increased tendency toward the employment of combinations to permit reduction in dosage of potent hypotensive components, although the availability of a large number of such ready-made preparations probably accounts for some of their popularity. A new potent ganglionic blocking agent, mecamylamine (Inversine), which may be more uniformly absorbed orally than hexamethonium, may obviate some of the disadvantages of this type of drug for the management of severe hypertension. Recent studies in animals suggest that in renal shut-down papaverine may be useful to overcome arteriolar constriction.

CENTRAL NERVOUS SYSTEM DRUGS

Probably the greatest current activity lies in the area of drugs affecting the central nervous system, where such terms as tranquilizer and ataraxic have been introduced to describe drugs which exert a calming rather than a sedative effect. Most of them relieve anxiety-tension states and some exhibit an antihypertensive effect in labile hypertension associated with psychogenic factors. Rauwolfia and its chief alkaloid, reserpine, have gained wide usage for this purpose and also, in combination with potent hypotensive drugs, for the management of severe hypertension. The phenothiazine compounds, chlorpromazine (Thorazine) and promazine (Sparine), the mephenesin-carbamate derivative, meprobamate (Equanil, Miltown), and an antihistamine-like compound, hydroxyzine (Atarax), are examples of drugs which exert either a primary or incidental tranquilizing effect that can be used to alter the mental outlook of patients. Their ultimate usefulness and effect in deep-seated psychoses requires further study. The use of hallucinogens, such as *d*-lysergic acid diethylamide (LSD 25) and mescaline, as chemical tools for testing the ability of new drugs to block experimentally induced psychotic manifestations may provide a future method for screening psychotherapeutic agents. More recent studies on the intravenous administration of bufotenine, *n*-dimethyl-serotonin, in human subjects indicate that it is hallucinogenic and that linear progression of symptoms occurs with increasing doses. Its effects are reminiscent of the effects of LSD 25 and mescaline, but develop and disappear more quickly (8). An amphetamine-like compound, pipra-

drol (Meratran), is employed as a cortical stimulant to combat depressive states not associated with marked anxiety or compulsive behavior. On the other hand, azacyclonol (Frenquel), the gamma isomer of pipradrol, is said to exhibit a tranquilizing action. Of more recent interest is a new cortical stimulant, methylphenidate (Ritalin) hydrochloride, which also may prove useful to counteract over-sedation and mental depression. The intense activity in this area holds some promise of future advances, but it is still much too early to offer enthusiastic predictions. Evidence is accumulating to support the view that the solution to the management of mental disorders lies in the further exploration of biochemical changes. Of passing interest is a new anticholinesterase, ambenonium (Mysuran), reportedly more effective and exhibiting fewer side-effects than neostigmine in the treatment of myasthenia gravis (9). Another compound of interest for this purpose, a dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide (Mestinon), is said to provide more uniform and longer action than neostigmine, and also may be used for diagnosis of the disease.

HYPNOTICS AND SEDATIVES

There are several mild hypnotic drugs which have been introduced to replace the barbiturates. They are chiefly useful to induce sleep. Some of them also have a weak sedative action that diminishes but does not abolish nervous tension. Among such drugs are ethchlorvynol (Placidyl), ethinamate (Valmid) chemically related to carbromal, glutethimide (Doriden), petrichloral (Periclor) a derivative of chloral hydrate, and methprylon (Noludar), a piperidine derivative. The employment of antihistamines as hypnotics or sedatives on the basis of their relatively marked sedative side action has not gained much support. However variations in the chemical structure of some antihistamines have revealed compounds having other useful depressant actions. For example the phenothiazine-derived antihistamine, promethazine (Phenergan), exhibits considerable activity against motion sickness, just as chlorpromazine (Thorazine) exhibits a marked antiemetic effect in addition to its tranquilizing action. The usefulness of antihistamines for nausea and vomiting of pregnancy (10) has not been established and their effectiveness for nausea and vomiting following surgery and anesthesia is variable.

GASTRO-INTESTINAL AGENTS

Among the gastro-intestinal agents, the introduction of an emulsifier, dioctyl sodium sulfosuccinate (Colace, Doxinate), for oral administration as a fecal moistening agent in the treatment of constipation is a recent contribution to the large number of drugs already available for this ailment (11). Its employment with mineral oil is theoretically inadvisable because emulsification of liquid petrolatum would encourage its absorption and deposition in mesenteric tissues.

HORMONES

In the hormone field the search for new drugs continues in two main directions: (a) new derivatives of the sex hormones that exhibit higher potency, and

those with actions not directly related to the reproductive system; and (b) new adrenal steroid compounds. A new androgenic compound, fluoxymesterone (Halotestin) is reportedly much more potent than methyltestosterone. Androgenic compounds such as methandriol (Metandren, Stenediol) and stanalone (Neodrol), like testosterone, exhibit a nitrogen-sparing anabolic action. Among them is a new derivative, norethandrolone (Nilevar), that is said to be free of masculinizing effects. Further investigation will be required to confirm this finding, and the search for such a compound is likely to continue. On the other hand, progesterone has been reported to induce loss of nitrogen—a catabolic action attributed to either a direct action on protein tissue or inhibition of anabolic hormones. A derivative of fludrocortisone, Δ^1, 9α-fluorohydrocortisone (DFF), which exhibits unusual corticotropin-suppressing activity has been used as a tool to study the amount of hydrocortisone which can be absorbed by the skin through depressing the stimulatory effect of corticotropin (ACTH) on the secretion of hydrocortisone by the adrenal cortex. By this method it has been shown that no more than 2 per cent of hydrocortisone is absorbed from an ointment applied to the intact skin (12). The 2-methyl analogs of hydrocortisone and fludrocortisone respectively have been reported to be much more potent than their nonmethylated cousins, apparently because the 2-methyl group reduces their susceptibility to enzymatic destruction in the body so that they are more slowly metabolized. The hydrogenated derivatives of cortisone and hydrocortisone, prednisone and prednisolone respectively, appear to induce less of the undesired physiologic effects of the glucocorticoids, but are not free of the tendency to provoke the development of asymptomatic peptic ulcer. Acetylsalicylic acid and its derivatives have not been replaced by the adrenal steroids in the management of the so-called collagen diseases, and recent studies have been initiated to learn more of the mechanism of action of salicylates in rheumatoid disorders. The antimalarial drug, chloroquine, used to control erythema in disseminated (systemic) lupus erythematosis, and the use of antileukemic drugs for the management of this disease, suggest further avenues for therapeutic investigation.

Further study of the physiology of the thyroid reveals the likelihood that this gland elaborates a second hormone, which has been identified as *l*-triiodothyronine (Cytomel). It appears to produce a more prompt, higher, but less enduring rise in the basal metabolic rate than does thyroxine. It probably offers no advantage for long-term management of myxedema over the more slowly-acting levothyroxine (Synthroid) or the cruder thyroid preparations, but may be useful when a prompt response is desirable. Apparently the serum protein-bound iodine level cannot be used effectively as a measure of metabolic status in patients under treatment with triiodothyronine.

MISCELLANEOUS DRUGS

The orally active hypoglycemic sulfonylurea derivatives, carbutamide (Orabetic) and tolbutamide (Orinase), which are under investigation for use in the management of diabetes mellitus in adults, will require extensive study to determine their value for this purpose (13). They provide a striking example of the

tremendous potentialities which lie in the pharmacologic exploration of modifications in the chemical structure of well known compounds. The non-bacteriostatic sulfonamide, acetazolamide (Diamox), which acts as a carbonic-anhydrase inhibitor and has a mild diuretic action, further illustrates the versatility inherent in the development of new compounds.

ANTINEOPLASTIC AGENTS

Antineoplastic agents are being given much more intensive study. Previously developed compounds are receiving increased application, in line with increasing awareness of their potential usefulness as palliatives, in addition to radiation therapy, for far advanced malignant conditions. For example, the use of nitrogen mustards, folic acid or purine antagonists and other antimetabolites in the leukemias has focused attention on their use in other types of malignancy. The nitrogen mustard, methchlorethamine (Mustargen), is being tried in the palliation of malignant effusion and may prove more convenient for this purpose than colloidal radioactive gold. A new nitrogen mustard, archlorethamine, [*p*-(*dl*-2-chloroethylamino)-phenyl-butyric acid], is under investigation for use in the treatment of chronic lymphatic leukemia. Investigation of nitrogen mustard as a potential palliative for primary or secondary liver neoplasms also has been suggested, because of its hepatotoxic effect when injected directly into the portal vein of rats. A new compound combining the antimalarial drug, chloroquine, with nitrogen mustard, also is under experimentsl study in types of malignancy involving respiratory and reticulo-endothelial tissues for which chloroquine has a special affinity. An isomer of adenine, [4-aminopyrazolo (3,4-*d*) pyrimidene, also called 4APP], has been shown to have antineoplastic activity in adenocarcinoma of mice (14). Among the many other compounds which are being screened for cancer may be mentioned a new purine antagonist derived from the carcinostatic antibiotic, azaserine, and chemically identified as 6-diazo-5-oxo-1-norleucine (DON). The new compound appears to be more potent than azaserine in the prevention of transplanted mouse sarcoma and this action is apparently increased by mercaptopurine (Purinethol). So far, its clinical effect does not appear to be particularly striking. A highly toxic antibiotic, actinomycin-D, also has been shown to exhibit a mild, temporary suppressive action against rhabdomyosarcomas and Hodgkin's disease. Sarkomycin, an antibiotic developed in Japan, also is being investigated for its sarcoma-inhibiting action in mice. A substituted desoxybenzoin compound, Amphenone, which depresses both adrenal and thyroid function by stimulation of the hypophysis, is under investigation as a possible means of suppressing excessive cortisone production in adrenal tumors. Developments so far appear to justify continued efforts to screen new compounds for the drug therapy of cancer. Interest in radioactive isotopes remains high in the midst of the search for non-radiation forms of therapy, and their development has permitted a much wider application of radiation technics.

IMMUNOLOGIC AGENTS

In the field of immunology, increased attention is being given to the development of active agents for immunization against infections for which no effective

or safe antigen has been found. The advent of the Salk poliomyelitis vaccine represents the result of more intense study of the immunology of viral diseases. An orally active attenuated live vaccine for poliomyelitis, composed either of a type I (SM) or a type II (TN) strain of polio virus and separately administered in capsule form to bypass the mouth and throat, is under study as another possible means of inducing active immunity to this crippling disease. It also has been given in milk to infants to increase the antibody titer provided by the prior administration of immune (gamma) globulin. The National Institutes of Health are said to have under investigation a live influenza virus vaccine. The present influenza vaccine is a killed suspension of representative strains which does not afford protection against antigenically different strains that may be encountered in all epidemics. The National Institutes of Health also are investigating a vaccine designed for protection against the APC (adenoidal-pharyngeal-conjunctival) group of viruses associated with upper respiratory infections. A new anti-tuberculosis vaccine also has been under experimental study in mice. New vaccines for rabies and for plague are under development, along with a vaccine for coccidioidomycosis. Of further interest immunologically is the development of a specific Treponema pallidum immobilization test for more precise serologic diagnosis of syphilis (15). Although complicated, and not yet employed by many laboratories, the test appears to be of value in the detection of false-positive and negative complement-fixation reactions and may offer a solution to this diagnostic problem in the management of syphilis. It does not appear to be of value as a criterion of cure. It is applicable also to spinal fluid, although a negative result does not rule out neurosyphilis (16).

SUMMARY

Trends in drug therapy currently are reflected by the type and variety of agents recently introduced for clinical use. Although new developments tend to follow patterns set by previous discoveries, modern methods for screening chemical and biologic agents as potential new drugs have extended the search over the entire range of therapeutics. Investigation also proceeds with greater intensity in those areas where satisfactory therapy is deficient or lacking. Current activity in this field reveals a predominant interest in drugs for the treatment of mental disease, which has been sparked by the development of compounds that exhibit a tranquilizing or ataraxic effect. A new crop of mild hypnotic agents also has appeared on the scene as substitutes for barbiturate hypnosis. In the hormone field there are continued efforts to find compounds with actions which do not affect the reproductive system. Exploration of new compounds for the drug therapy of cancer is proceeding with similar vigor. Previously developed antineoplastic agents also are being restudied as palliatives in various types of malignancy. The investigation of the problem of atherosclerosis continues in the direction of measures designed to combat hypercholesterolemia. The search for less toxic and potent hypotensive agents proceeds in the area of cardiovascular disease. Previous progress in the antibiotic field and the chemotherapy of infections in general, has not slowed efforts to find new and improved anti-infective

agents. Progress in this field also lies in the direction of prophylaxis through the development of new and better active immunizing agents.

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NEW CLINICAL PRODUCTS OF BLOOD FRACTIONATION: THEIR THERAPEUTIC IMPLICATIONS AND USE*

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The title of this essay was amended from "New Clinical Products of Plasma Fractionation" to "New Clinical Products of *Blood* Fractionation." For a society as eminently interested in therapeutics as this one, it would be wasteful indeed to discard the cytologic fraction, which is roughly 50 per cent of each unit of blood. Unfortunately this practice has been diffidently accepted by the very agencies charged with responsibility for the blood needs of this country. Beginning in World War II and continuing right up to the present day, every unit of blood earmarked for fractionation purposes has been characterized by the initial discard of the red cell mass. This is a waste which cannot be tolerated in a country where blood is in short supply. As will be developed later in this presentation, there have been adequate reasons for such a procedure—primarily, lack of ability to preserve erythrocytes beyond three weeks and to separate them under sterile conditions. Fortunately, we are now on the threshold of an entirely new era in cell preservation and separation techniques, so that this waste no longer need obtain.

It is scarcely necessary to outline the benefits of blood fractionation. Not only are many products made available that otherwise could not be obtained, but the overall economy is greatly enhanced by reserving specific blood components for those clinical conditions in which they are needed, thus avoiding the waste involved in a transfusion of whole blood. There is only one condition in which whole blood is specifically indicated, *viz.*, the treatment of hemorrhagic shock, and the requirement for this purpose has been estimated to comprise slightly less than 50 per cent of the total transfusion requirements of civilian hospitals. Moreover, even here, it is not whole blood that is needed, but rather a combination of red cells and a plasma volume expander. The gamma globulins, lipoproteins, leukocytes and many other fractions are totally without value in hemorrhage. In these days of increasing realization of the value of blood components, it is somewhat surprising to recall that the history of fractionation goes back only to World War II, when methods of desiccation permitted the prolonged storage of plasma in a powdered state for use by the Armed Forces. The sudden impetus of World War II focused scientific attention on the potential benefit of fractionation. Largely under the aegis of the late Dr. Edwin J. Cohn, an entire pattern of protein extraction was devised which yielded increasing numbers of blood products of potential therapeutic value. The first of these, albumin, permitted the use of that portion of blood which had the selective osmotic effect of

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drawing fluid from the tissues and preventing or mitigating shock. This was followed in rapid order by antihemophilic globulin, purified fibrinogen, various types of fibrin foam and last but not least, gamma globulin. In this day of widespread use of gamma globulin, it is worth pausing a moment to pay tribute to the keen foresight of the late Dr. Edwin J. Cohn. The original Armed Forces subsidies which financed his plasma fractionation program called for target research specifically aimed at the recovery of albumin. When Dr. Cohn pointed out the therapeutic possibilities of the by-product, gamma globulin, and refused to discard it as directed by governmental contract, he was deprecated as an impractical dreamer. At a meeting of one of the philosophic societies in 1944, he predicted the specific prophylactic value of gamma globulin in poliomyelitis, infectious hepatitis and measles, yet a delay of many years occurred and the originator has been generally overlooked.

By the close of World War II, some half dozen blood products were available for clinical use. At this same time, however, with a return of service men and other blood donors from groups wherein inoculations and needling had been widespread, there was a sharp rise in the potential infectivity of dried plasma and of each of the plasma products, with the single exception of albumin, which was so stable that it could be pasteurized during production. Commercial methods necessitated the pooling of plasma prior to fractionation, thus greatly magnifying the potential infectivity. This led to a plasma-induced incidence of homologous-serum hepatitis which reached as high as 20 per cent early in the Korean War. Ultraviolet irradiation, cathode-ray, and other means of sterilization were only partially protective. As a result, the use of blood products fell into temporary disrepute. There was a flurry in the direction of the so-called "blood substitutes" or plasma volume expanders. A discussion of them is not germane to this presentation; suffice it to say they, too, presented significant problems, particularly in the fields of sensitivity, anaphylaxis, and foreign-body reaction. Moreover, as we have more recently learned, there were bleeding tendencies secondary to coating of the platelets by dextran, thus reducing the effectiveness of thrombocyte plugs at any break in the integrity of the vascular bed.

Concurrent with these developments, there has again been major progress in the area of blood fractionation, due mainly to four factors: 1) realization that survivors of atomic radiation require not only expansion of plasma volume but also red cells, platelets and leukocytes to support the bone marrow depression; 2) realization that whereas ultraviolet irradiation of plasma to remove hepatitis virus is ineffective, the same treatment can be used successfully if applied to the blood fractions in their isolated, more stable state; 3) realization that new chemical methods of metal interaction improve the stability of the end-products and simultaneously reduce the cost of processing; and 4) realization that new centrifuge methods predicated on prompt isolation of the cells from their plasma substrate will yield products of increased stability and therapeutic value.

NEW TECHNIQUES OF BLOOD SEPARATION

What are the new techniques of blood separation? Two procedures in particular deserve mention: the new closed-system centrifugation of Cohn, and the

zinc fractionation of resin plasma. Only brief mention will be made of the principles of the new Cohn Fractionator. This equipment already has given rise to significant improvement in separation and preservation of the formed elements of blood (1–5). Its use in plasma fractionation is still at an experimental level but, here too, it possesses certain features of closed-system operation (such as control of gas tension) that give promise of improved stability of lipoproteins and certain coagulation proteins. This apparatus was developed as a direct result of a Blood Congress held in Boston in 1949, at which there was general agreement that standard methods of blood collection were sufficiently traumatic to obviate recovery of any fractions except the more stable ones such as albumin, gamma globulin and erythrocytes. The new centrifuge was designed to improve the collection and separation of blood by incorporation of physiologic (nonwettable surfaces), continuous-flow separation (in order to decrease gravitational force within the centrifuge), ion exchange decalcification (to permit the use of the new Method 12 of metal interaction for subsequent protein fractionation), direct collection of donor blood in the equipment (to shorten the exposure time of the individual cell strains to proteolytic enzymes), and immediate cooling (further to diminish enzymatic degradation).

The schematic diagram in Figure 1 shows the principles of continuous-flow separation. Blood enters from below by gravity feed, having first passed through a resin column and heat exchanger. It enters the apex of the inverted bowl and fans out to the periphery with gradual acceleration thus avoiding foaming or turbulence. The film of blood flows downward through the centrifugal field. The heavier red cells remain in the upper compartment and the lighter plasma overflows into an individual container below the revolving bowl. The dimensions are such that completion of a one-pint phlebotomy from a normal hematocrit donor

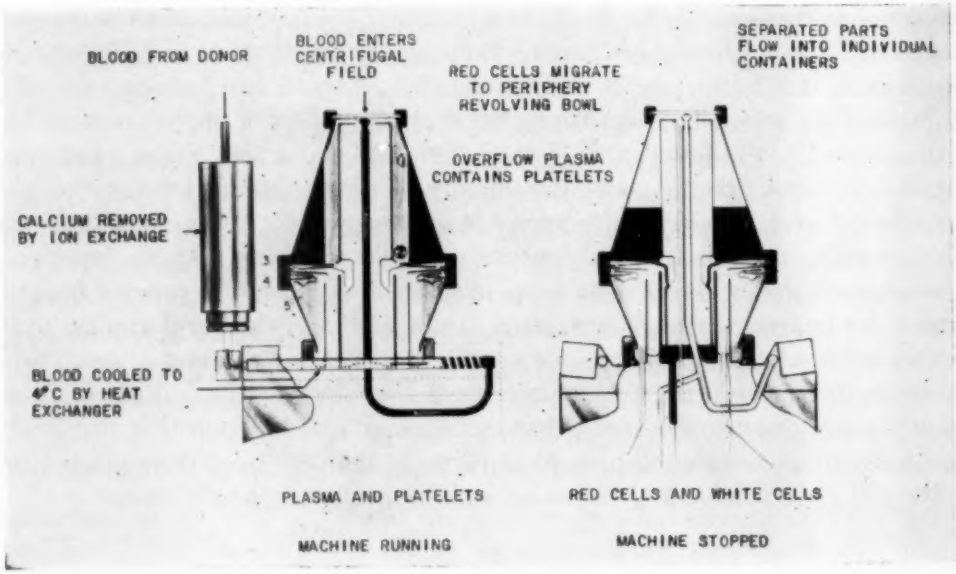
BLOOD FROM DONOR
BLOOD ENTERS CENTRIFUGAL FIELD
RED CELLS MIGRATE TO PERIPHERY REVOLVING BOWL
SEPARATED PARTS FLOW INTO INDIVIDUAL CONTAINERS
OVERFLOW PLASMA CONTAINS PLATELETS
CALCIUM REMOVED BY ION EXCHANGE
BLOOD COOLED TO 4°C BY HEAT EXCHANGER
PLASMA AND PLATELETS
RED CELLS AND WHITE CELLS
MACHINE RUNNING
MACHINE STOPPED

FIGURE 1

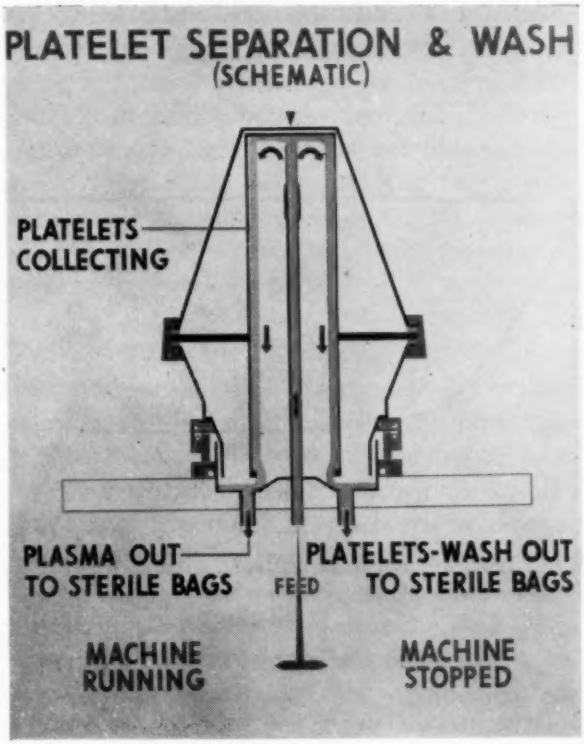

FIGURE 2

will leave a unit of packed red cells and their entrained white cells in the upper compartment. The machine is then decelerated and the packed cells are collected separately. In the event one wishes platelet removal, the plasma is then forced under positive nitrogen pressure into a second revolving bowl (Fig. 2) which contains a falling film insert. The capacity of this bowl, dependent on the bottom weir, is about 25 cc. The flowing plasma in this instance again fans out from the apex of the inverted bowl and falls downward through the centrifugal field. The distance individual platelets must move to be out of the falling film field is reduced to a few millimeters, thus permitting isolation of these low density cells with minimum gravitational force and no significant packing.

The effluent cell-free plasma from this type of machine separation is totally different from plasma collected under ordinary conditions. The stability of its proteins is infinitely improved by removal of all cells and by the prompt cooling which has taken place. Moreover, the absence of citrate ion or metal-complexing agents has made possible the development of a totally new system of protein fractionation. In 1950, Cohn and collaborators (6) found that the addition of heavy metals to resin plasma would cause a prompt precipitation of the unstable globulins, glycoproteins and coagulation proteins which formerly precipitated in the old Fractions I + II + III with the alcohol technique. In Figure 3 the optical density of a plasma specimen is plotted on the ordinate against zinc and mercury concentrations. It may be seen that in the range between 10 and

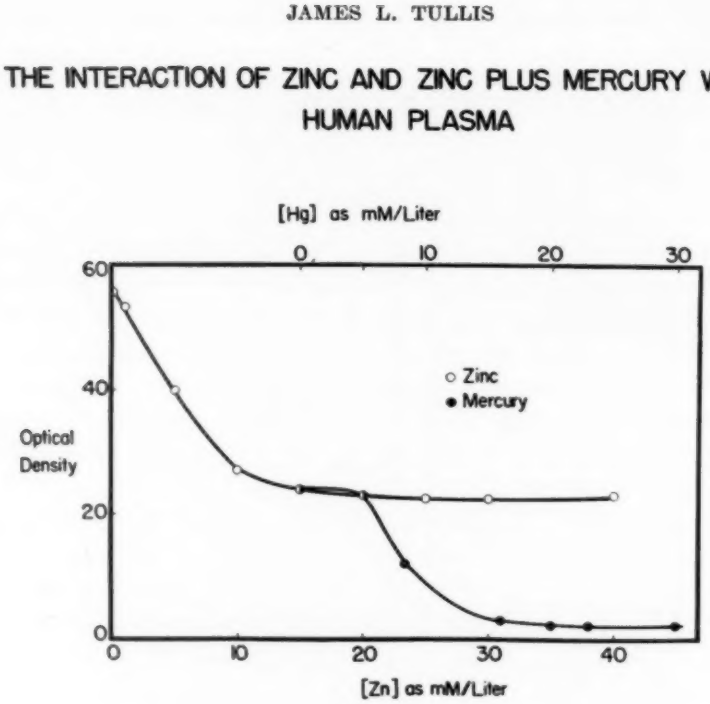

FIGURE 3

40 mM/L of zinc diglycinate, there is a consistent reduction in optical density concurrent with flocculation and precipitation of all of the globulins.

PRODUCTS OF BLOOD FRACTIONATION

To what products have these new methods given rise?

I. *Stable plasma protein solution (SPPS)*

The supernatant solution after zinc precipitation is referred to as SPPS (Stable Plasma Protein Solution). It contains all of the albumin and A-lipoprotein in a stable form. By a single chemical step, therefore, it is possible to prepare a solution containing most of the necessary osmotic proteins for use in treatment of shock, with separate precipitation of a paste from which one later can remove other proteins which have demonstrable clinical effectiveness. SPPS is currently undergoing clinical tests in the Boston area and more widespread evaluation of this product is anticipated in the near future. Like albumin, which is its major constituent, it may be pasteurized and thus can be rendered free of hepatitis virus. Its potential advantages are simplicity and economy of production, stability (does not require refrigeration) and species specificity (no danger of delayed foreign protein reaction). SPPS can be made from ordinary citrated blood. It is questionable, however, whether SPPS would have been discovered without the use of ion-exchange plasma free of metal-complexing agents.

II. *Gamma globulin*

The globulin precipitate obtained by the zinc method for preparation of SPPS has not undergone clinical evaluation. Although the antibody-containing gamma fraction can be extracted from this protein paste, experimental injection of such

globulins from a pool of icterogenic plasma showed contamination with hepatitis virus. This has delayed the clinical use of the zinc method until the stability of the globulins can be improved sufficiently for heat pasteurization. Thus, the commercially available gamma globulins are still made by the cold-ethanol methods developed during World War II. The therapeutic utility and indications for this product are so well known they do not require discussion here, except to note that gamma globulin exerts protection against the virus of infectious hepatitis but not against the virus of homologous-serum hepatitis. The reason for this paradox remains unexplained.

III. *Antihemophilic globulin*

Of perhaps equal potential significance, although not yet at the level of clinical testing, is the increased stability and purity of certain coagulation proteins derived from resin plasma, *viz*, antihemophilic globulin, prothrombin and Ac-globulin. The original antihemophilic globulin preparations of the late 1940's were beset with variation in potency, and instability on storage. On the basis of present evidence, it seems likely that a significant part of this difficulty was due to the lapse of several days between blood collection and fractionation, during which time interaction continued between the platelets and the antihemophilic factor. The present method of immediate removal of all cells within the Cohn Fractionator has given rise to cell-free plasma with consistent antihemophilic activity. Such platelet-free plasma may be stored for later direct use or can be further fractionated to yield a new, relatively pure, antihemophilic preparation. This new product, reported by Surgenor and Walton (7), gives promise of being very valuable in the management of hemophilia. The method of production consists of exposure of the plasma to barium sulfate for adsorption of prothrombin, PTC and SPCA, followed by precipitation of Fraction I with 6 per cent ethanol at pH 6.8. Fraction I is then redissolved in .15 M salt, pH 7.0, and high molecular weight dextran sulfate is added. The dextran selectively forms a complex with fibrinogen, leaving a supernatant solution containing relatively pure antihemophilic factor. The supernatant material is then dialyzed, and a euglobulin precipitates. This globulin is soluble in saline and contains antihemophilic factor in a concentration approximately 200 times that of the native plasma.

IV. *Fibrinogen*

The new fibrinogen products are not a direct outgrowth of the foregoing research. The newly released fibrinogen merits reference at this time, however, as it is still in an early stage of acceptance by the medical profession at large. The indications for its use require further delineation, in order to avoid abuse of the product in hemorrhagic states which are not secondary to fibrinogen deficiency.

The original fibrinogen preparations developed in 1945 fell into disrepute because of contamination with the virus of homologous-serum hepatitis. Through the persistence of Dr. Harlan Anderson of the Michigan State Laboratories, and concurrent research by scientists in some of the commercial pharmaceutical

firms, however, this problem seems to have been largely overcome. By the addition of high concentrations of glucose, the isolated fractions of fibrinogen can be subjected to moderately high levels of ultraviolet irradiation without denaturation. The new commercial fibrinogen preparations with which you may be familiar, carry a required statement on the label cautioning against possible hepatitis contamination, but in a recent report of Dr. Anderson's covering 300 doses administered to 131 patients (8) only 1 case of jaundice was observed, and this could have been attributed to the concurrent transfusion of blood. What are the indications for use of fibrinogen? Obviously, it should be given only in the presence of a reduced level of fibrinogen in the circulation. Chemical determination of circulating blood fibrinogen is sufficiently complex and the need for control of hemorrhage is so urgent, however, that this test often cannot be made. A handy bedside technique has been reported by Dr. Roy Bonsnes; it consists of the simple addition of thrombin solution to a blood sample, and observation of coagulation time. The most important factor in control of afibrinogenemia is probably the development of sufficient clinical acumen to suspect its presence. Clinical awareness of this condition began with the work of Drs. Wiener and Reid at the Boston Lying-in Hospital (9). Afibrinogenemia can occur in obstetrical, medical, surgical and pediatric practice, as follows:

Obstetrical. There are three major causes of afibrinogenemia in this group. 1) Amniotic-fluid emboli. Dr. Reid's first case was of this type; at postmortem examination there were large emboli of amniotic fluid in the pulmonary tree of a young girl who died of sudden exsanguination during labor. It was found that amniotic fluid possesses marked thromboplastic activity and that this had been known for many years, but forgotten. The mechanism of bleeding is postulated as due to the release of so much thromboplastin into the circulating blood from dilated uterine sinusoids that blood fibrinogen is utilized intravascularly faster than new fibrinogen can be produced by the liver. 2) Prolonged carriage in the uterus of a fetus dead because of Rh or other blood group incompatibility. It is believed that the excessive proteolysis which accompanies retention of the dead fetus results in sufficient fibrinolytic activity to exhaust the blood fibrinogen. 3) Premature placental separation. As in the case of amniotic-fluid emboli, thromboplastic substances can be rapidly absorbed by the dilated uterine veins before contraction.

Surgical. Afibrinogenemia can follow any type of extensive surgical operation, particularly if major blood replacement has taken place. Thoracic surgery, in particular, has a noticeable incidence of this complication.

Medical and pediatric. Medical and pediatric causes of afibrinogenemia are primarily confined to mismatched transfusion reactions and to the rare case of congenital absence of fibrinogen.

V. *Properdin*

In August 1954, Dr. Louis Pillemer and collaborators at Western Reserve University announced the discovery of a new protein which they named pro-

perdin. This substance appears to be an integral part of the natural immune defense of the body, is independent of the leukocyte and antibody systems, and has to do primarily with the natural virucidal activity of fresh serum.

It was discovered during attempts to purify the C^3 component of complement. When adding a yeast polysaccharide, zymosan, to serum at +37°C., Pillemer *et al.* found that the third component of complement is inactivated (10). If, however, they added a similar zymosan preparation at +17°C. and removed the insoluble residue, a material could be eluted which was distinct from complement (requiring magnesium ion for activation) and which contained potent *in vitro* activity against viruses, certain bacteria and red cells. The material was named properdin. Current studies from many laboratories suggest that there is a relationship between serum properdin levels and the resistance or susceptibility of experimental animals to irradiation, surgical shock and/or infection. It recently has become possible to isolate properdin from plasma as well as from serum (11). The plasma must be ion-exchange collected, again demonstrating the advantage of absence of ordinary citrate or oxalate in routine blood collection.[1]

VI. *Ceruloplasmin*

This copper-containing protein with a faint blue-green color has been used experimentally by Scheinberg and Gitlin (13) in a case of Wilson's disease (hepatolenticular degeneration with pseudocirrhosis of the liver). Not enough material has been utilized to warrant conclusions regarding clinical effectiveness.

VII. *Iron-binding globulin*

This material is familiar to many of us because of its use in investigative studies. It is the selective protein of plasma which transports iron. Measurement of its degree of saturation is of clinical value in the differentiation of anemias as well as in the differentiation of certain liver diseases, notably infectious hepatitis and Laennec's cirrhosis. Recently, it has undergone experimental trial as a therapeutic agent in the treatment of one of the blood dyscrasias. Evidence of its potential value remains to be established, but the status of investigation is sufficiently encouraging so that all of the supplies from the pilot plant at Protein Foundation Laboratory have been temporarily committed for this study.

VIII. *Leukocytes*

The leukocytes may be dismissed with the simple statement that it is unlikely they will ever be available for *in vivo* use in the treatment of leukopenia. The *in vitro* life span of these cells is so short, that even if one had large supplies of preserved leukocytes, it would take almost all of the people all of the time to supply one of the people some of the time. Preserved leukocytes can be maintained for *in vitro* studies (14) but, even under optimal conditions, the maintenance time outside the body is only about two weeks.

[1] Since preparation of this manuscript, further work of Pennell (12) has uncovered a technique for the recovery of properdin from standard ACD blood.

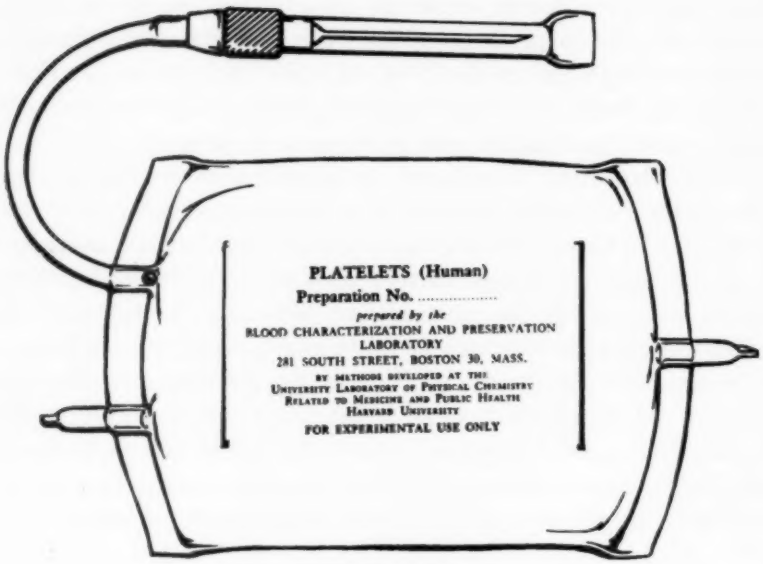
PLATELETS (Human)
Preparation No. .....
prepared by the
BLOOD CHARACTERIZATION AND PRESERVATION LABORATORY
281 SOUTH STREET, BOSTON 30, MASS.
BY METHODS DEVELOPED AT THE
UNIVERSITY LABORATORY OF PHYSICAL CHEMISTRY
RELATED TO MEDICINE AND PUBLIC HEALTH
HARVARD UNIVERSITY
FOR EXPERIMENTAL USE ONLY

FIGURE 4

IX. *Platelets*

Platelets represent a different story. It has been possible to isolate these cells in relatively pure strain in the apparatus previously described. Resuspension of such washed platelets in a solid mold of gelatin, free of any coagulation proteins with which they can interact, has led to a stability which permits preservation for at least a year. The cells are stored in a plastic container ready for immediate use *in vivo* (Fig. 4). Such preserved platelets possess potent thromboplastic activity, as assayed both *in vitro* and *in vivo*. Their most significant value probably is the immediate availability for transfusion purposes at the time of emergency thromboplastic hemorrhage (15). They are administered within red cell type, and the only preliminary screening necessary is that of a platelet antibody test to demonstrate the absence of autoagglutinins (16, 17).

X. *Erythrocytes*

Finally, we turn to something which is not a trace component. Red cells have entered a new era from the standpoint of therapeutic potential. Reports by Mollison and Sloviter (18), Sloviter (19), Lovelock (20), Brown and Hardin (21), and others have fully established that red cells previously glycerolized can be stored in the frozen state (with satisfactory subsequent *in vivo* survival) up to one or two years. The major obstacle which has obviated translation of this fundamental discovery into clinical practice has been the desirability of removing the glycerol prior to retransfusion. The Cohn Fractionator possesses unique adaptability to this process because of its closed-system sterility and continuous-flow principles. Modification of the bowl of this centrifuge so as to include long-traverse washing of red cells has made possible the smooth dialysis of glycerol out of red cells after thawing. Current studies on the use of the equipment for

this purpose are in progress in the Boston area. Already, some 50 bloods so processed have been transfused, with *in vivo* survival in as high as 92 per cent. It is entirely probable that this type of processing and preservation will be generally practiced within the immediate future. If so, the previous problems of rare cell types can be eliminated by long-term banking methods, and the profligate wastage of red blood cells concurrent with plasma fractionation need no longer obtain.

SUMMARY

This presentation is a discussion of new techniques of blood separation and the resulting products—stable plasma protein solution, gamma globulin, antihemophilic globulin, fibrinogen, properdin, ceruloplasmin, iron-binding globulin, leukocytes, platelets and erythrocytes.

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THE PRESENT SHORTAGE OF HOSPITAL NURSING PERSONNEL AND THE RESPONSIBILITY OF THE DOCTOR*

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There are few hospitals that are not experiencing shortages in nursing service at the present time. This has become so acute in some communities that it has been necessary to close entire nursing units, thus adding to the problem of providing an adequate number of hospital beds in the community. Adequate patient care cannot be maintained at a safe level with the presently available hospital nursing staff. Human beings can be pushed just so far and then they rebel. Our present economic structure is such that hospital nurses and auxiliary nursing personnel can find employment—often with greater income and certainly with greater potential security—in related medical fields, and they frequently transfer to these positions when the tension and the pressure of work becomes too great in our hospitals.

THE INCREASED DEMANDS

The requirements for nursing and nursing services have expanded and are continuing to expand faster than the supply of nurses is increasing. There are many reasons for this. There is a notable increase in our population, with a constantly higher percentage of older members who require more medical attention. A continuing prosperity and high employment have allowed more people to seek hospital care, and the increases in prepayment plans and disability insurance have enabled them to help pay for it. In 1940, the number of people in the United States with hospital insurance was 12,312,000; in 1951 it was 85,991,000; and in 1954 it reached a new high of 101,494,000 (1). This represents an increase of over 800 per cent in fourteen years. In 1954 the growth rate of hospital insurance was over two and a half times as rapid as the rate of growth of the population as a whole. Advances in medical science and education of the public have made people increasingly aware of the advantages of hospital care. New hospitals are being built and additions are being added to thousands more. The number of nurses in the Armed Forces has increased by approximately 5,000 since 1949 (2). The constant increase in new and better medical techniques has increased the duties of the nurse, as well as the complexities of these duties. Moreover, the shortage of interns has resulted in more duties being delegated to nursing personnel, particularly in the smaller hospitals. The patient's stay in the hospital has been reduced from 15.9 days in 1945 to 7.9 days in 1953 (3). This increases the number of patients cared for and the frequency of the first few critical days when the most skilled nursing is needed. Higher educational standards for

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student nurses have resulted in more teaching and supervision and have permitted less time for bedside nursing. The forty-hour week has necessitated approximately a 20 per cent increase in nursing personnel of all kinds (2). These are but a few of the most obvious reasons for the increased demand for nurses and nursing services.

There are more nurses employed, and there are more students enrolled in schools of professional and practical nursing than ever before in our history. There are nearly 400,000 registered professional nurses and 100,000 licensed practical nurses actively engaged in nursing (3). There are 103,000 students enrolled in schools of professional nursing and 10,000 in approved schools of practical nursing. The most conservative estimates place the number of professional positions for nurses waiting to be filled at 50,000, and it has been recommended that 60,000 practical nurses be added to the nursing force of the nation annually in order to try to keep up with the demands for patient care (3).

SOME SOLUTIONS OF THE PROBLEM

The remedy for this serious situation is not a simple one. To help alleviate the problem, the National League for Nursing was founded in June 1952 by the fusing of 7 national nursing groups, 3 organizations and 4 committees. The American Medical Association, the American Nurses Association and the American Hospital Association are working closely with the National League for Nursing, and an intensive recruitment program is under way. It has been the experience over the past ten years that this program must be conducted at the national level as well as at the local level. The local program must be reinforced by the national program to promote the most favorable impression about nursing as a career in the minds of the young people, as well as their parents and counselors. Physicians frequently have an opportunity to advise young people, and it is due to their counsel that many young women enter the nursing profession. Frances P. Bolton, congressman from Ohio, proposes the establishment of a national commission on nursing services to study the entire situation. This could be very helpful, but it will require many months of study and it does not take care of our present dilemma. Some measures must be taken at once to try to solve part of the problem at the local level. Naturally, directors of nursing and hospital administrators must see to it that all personnel are being utilized at the very highest level of their skill and ability. Physicians also have a responsibility in trying to conserve the time of the nurse and other hospital aides. Even such simple things as reviewing daily orders for patients, discontinuing and avoiding unnecessary orders, facilitating prompt discharges, cooperating with the standardization of supplies and equipment, and using stock items whenever possible will decrease the work load many hours in the course of a week. Individual studies have shown that 40 to 50 per cent of nursing time and 50 to 60 per cent of nursing effort could be redirected to the specific care of the patient through provision of more adequate and efficiently planned facilities and equipment, and through use of more effective and efficient work methods (4).

All these things will not help the immediate situation unless we also make an

additional effort to improve the morale of the nurse and the nursing personnel. We can all be part of such a program. Most nurses enter nursing schools with high ideals and a desire to be of service. They continue in the nursing field for the same reason, and they expect to be part of a "medical team," a team in which all members are treated with respect. Unfortunately, either within the nursing staff itself or within the medical or intern staff, tensions develop when the work becomes unusually heavy, and these tensions can lead to criticism. Such criticism sometimes may be necessary and justified, but frequently it is misdirected and unjust. These things happen in all walks of life and normally can be understood, but it becomes much more serious when people are greatly fatigued and overworked. When this occurs frequently during the day, it may lead to discouragement and frustration of such a degree that either some relief must be found, or a member of the "medical team" finds it necessary to resign or end her nursing career.

It has been my pleasure over a period of many years to be in charge of a Nurses' Health Service in a hospital of about 550 beds. The nursing school in 1955 had approximately 250 students and there were about 190 graduate nurses on the nursing staff. The Health Service is maintained as a unit on one floor of the hospital. The Health Service Supervisor has her office in this unit and there are two consultation rooms for physicians. The infirmary, which is adjoining, has twelve beds—two two-bed rooms and two four-bed rooms. Two medical residents act as Health Service physicians and have office hours at 7:30 A.M. and 3:00 P.M. each week day. When the students enter the school, they are assigned in rotation to internists on the hospital staff who have indicated their willingness to participate in the Health Service program. The student nurses are seen by the resident physician when they report on sick call and are only referred to the staff physicians for care when they present some unusual problem or when they are admitted to the infirmary. The entire medical staff is available for consultation when needed. During the course of a year, there are approximately 5,700 visits to the Health Service, or an average of about 23 visits per week day. Many emotional problems develop in such a group, and it has always been the policy of the Health Service to try to treat such problems with sympathetic understanding. Because of this attitude, we have gained the confidence of the nurses, and it has given us an insight into some of the traumatic experiences that these girls suffer during an ordinary day in a busy, understaffed hospital.

A well qualified Nurses' Health Service supervisor is a tremendous asset in such a program. Our supervisor works closely with the educational department of the School of Nursing, and she teaches personal health and hygiene in the nursing professional adjustment classes. Emotional problems in the freshman student nurse group develop largely from their difficulty in leaving home and their need for becoming self-reliant adults in greatly different surroundings, where responsibility must be accepted. They also have all the problems of any teen-age girl going to college. They are assigned counselors in the school to help them with their educational program, but the Health Service supervisor is con-

sulted often about their home and personal problems, which seem exaggerated when the educational program becomes difficult. Usually, it is only necessary to be a good listener, offer a few constructive suggestions and refer the student back to her counselor. Occasionally, this is not possible, and it then becomes a problem for the Health Service. The Health Service supervisor handles most of such matters in consultation with the Director of Nursing and the Health Service physician, unless hospitalization is necessary or specific medical advice seems indicated. In such cases, a staff physician is consulted. It is important to have the students realize early in their nursing program that there are understanding people to talk to in the hospital and that the hospital community is not entirely a "wall of discipline." Most student nurses will continue their nursing education when a little intelligent guidance is given during such difficult adjustment periods.

When the students start working on the nursing units of the hospital, they must be supervised very rigidly. Guidance is provided by the nursing staff, but physicians can do a great deal by talking to the nurses about their patients when making rounds. It takes only a few minutes to point out some of the interesting details of patient care and to stimulate the nurse to learn more about the patients under her care. This is a far better way to increase morale and to encourage better nursing care for hospital patients then to make caustic remarks or to write insulting notes on the charts when nursing procedures have been inadequately carried out or misunderstood. I have collected from the hospital charts a few notes merely to show a destructive method of criticism. "This patient is improving in spite of poor nursing care." "We would appreciate it if the orders on this patient would be carried out. Is it necessary to have a special nurse to get these tests done?" "You might notify the 'powers that be' that this patient is leaving the hospital because of poor nursing care." Actually, in the latter case, a representative of the hospital went to the home of the patient to investigate the problem, and the patient stated that she left the hospital because she was displeased with her medical treatment. I am not attempting to criticize either the nurse or the physician, but merely to try to emphasize the need of a "medical team" to work together for a common interest, namely, the hospital patient. Repeated criticism of this type only adds to the burden, and disrupts morale within the nursing department.

At times there are serious matters which must be corrected. This is welcomed in any progressive institution. It is unfortunate, however, when corrective measures are not taken up through proper channels. It does no good to reprimand a member of the nursing staff who is not the responsible person, or to discuss the matter before the patient, when all that is gained by so doing is to undermine the administration of the hospital, the Director of Nurses or the nursing staff in general. It is not unusual to lose members of the graduate nursing staff of the hospital or to have student nurses seek medical consultation in the Health Service following such episodes. By intelligent example, the attending physician can teach the resident and the intern staff how to handle such matters, and to instill in them the desire to instruct or to correct the nursing personnel in a kindly and friendly way when this is necessary. Hospitals are only as good as the people

that staff them, and a helpful, cooperative and constructive attitude should be an ever-guiding influence in such institutions.

SUMMARY

There are many conflicting views as to what is the best way to solve the present shortage of hospital nurses. While these differences of opinion are being discussed and debated, all physicians should begin at once in their own hospitals to use the present available nursing staff to the best possible advantage, and to help in the recruitment program.

Physicians should also increase the efficiency of the nursing personnel by improving their morale and by making them a part of the "medical team." Cooperation in reducing unnecessary nursing procedures and in using standard hospital methods will help to make the load somewhat easier. More detailed instructions and more adequate explanations, when special procedures are indicated, will stimulate interest in the care of the patient and will decrease misunderstanding. Orders should be plainly and completely written, and residents and interns should be taught the importance of the cooperative care of the patient.

A well organized Nurses' Health Service is an important adjunct in promoting security, improving morale and adding stability to the entire nursing staff. High quality medical and nursing care given in the Health Service and in the Infirmary will be multiplied many fold when it is redirected into hospital patient care.

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THE TEACHING OF THERAPEUTICS IN GRADUATE AND POSTGRADUATE MEDICAL EDUCATION*

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Inasmuch as this essay could very well be entitled, "The State into which the Teaching of Therapy Has Fallen," it would seem most appropriate to define terms of reference at the very outset. Therapeutics in its widest interpretation encompasses the entire spectrum of treatment—drugs, medicinals, antibiotics, biologicals, surgery, physical medicine, dietetics, psychotherapy, and all of the others, the exhibition of which contributes to the welfare of the patient. However, for the purposes of this paper we shall confine our interest to medicinal therapy, *i.e.*, drugs, biologicals, and antibiotics, inasmuch as the other fields comprise specialties in themselves. Further, we shall limit our field of consideration to graduate and postgraduate education—the levels of endeavor at which the teaching of therapeutics should be most productive and should capitalize on the basic foundations laid in medical schools.

It would seem significant that in surveying source material, I found comparatively few articles in the indexed literature which were pertinent to the subject as we have defined it, and none published later than 1946. Most of those that have appeared dealt wholly or predominantly with the field of undergraduate training. Of course, much has been written on individual therapeutic agents and methods per se, but few on over-all teaching interest.

The frequency of the indexed writing on teaching of therapeutics from 1799 to 1946 fits neatly and chronologically into a normal curve of distribution, the peak of incidence occurring in the early 1900's. The real upcurve begins in 1896, preceded by only two references, one in 1859 (1) and the other in 1880 (2). The absence of papers prior to this time coincides with the era of the "School of Therapeutic Nihilism," delineated by Major (3) as having existed from 1830 to 1850. The down-curve, the present era of scant attention, might aptly be labeled the "Era of Therapeutic Plethora," with the present diminished interest in therapeutic instruction representing a reaction—a typical plethoric manifestation.

To bring our consideration rapidly up to the present, I have been constantly amazed by the scant knowledge of therapeutics displayed by many of the physicians who come for training in the various specialties. All of these men are graduates of good medical schools, all have had at least one year of internship in a reputable hospital approved for such training, and some have had one or more years of resident training. Almost universally, they display a lack of fundamental knowledge of drug actions, incompatibilities, dangers, toxic reactions,

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and even in some cases, dosage. It is indeed difficult to understand how those having the level of intelligence necessary to complete satisfactorily the required courses in our medical schools can fail to realize the importance of drug therapy in their future careers. No matter what field the physician selects as his specialty, it is necessary that he be basically a good physician, and a good physician must have a sound knowledge of the modes and methods of therapy of the associated disciplines of medicine.

FACTORS IN THE NEGLECT OF THERAPEUTICS

In discussions with other directors of medical education I have found that the dearth of knowledge concerning therapeutics is not confined to any one institution or group of institutions. In fact, the problem could easily become Topic A in our conversations, were it not for the more immediately pressing problems of changing Board requirements, accreditation maneuvers, resident selection, and the like. The de-emphasis on teaching of therapeutics is so much with us that it would seem logical to ask the origins. Although undoubtedly there have been many factors that have interacted to produce the situation, two principal elements present themselves immediately—the dramatic developments in medical science during the past few years, and the remarkable advances made in pharmaceutical manufacturing during the same period.

With the recent achievements in the science of medicine, educational emphasis has naturally been placed on diagnosis, physiologic-pathologic mechanisms, biochemistry, and biologic developments. With this shift in emphasis, the teaching of medicinal therapy has naturally diminished in relative importance. In view of the dominant place that the practice of therapeutics has in the care of the patient, this shift of emphasis is somewhat paradoxical. Yet, when planning a program or a postgraduate course or editing a journal, with time and space in great demand, who would feature drug therapy when more currently dramatic subjects compete for listener or reader interest? What co-ordinator of a graduate training program could stand the onslaught of educational "demands" and permit more than a few token hours for teaching of therapy? Even the Specialty Boards, with few exceptions, presume that the applicant knows basic medicinal therapeutics and concentrate their efforts on more provocative areas of diagnosis, pathology, physiology, and biochemistry. To me these are the marks of expediency and the lines of least resistance, of which we must constantly be aware and about which we must do something if the paradox is to be resolved.

The second significant factor in the downgrading of the subject of therapeutics has been the seemingly decreased need for the physician to understand the actions, the mechanisms, and the dangers of drugs, as a consequence of the development of the manufacturing pharmaceutical industry, which in the course of events has simplified to the point of incredibility the actual rationale of prescribing. With the perfecting of manufacturing and packaging methods it is only logical, therefore, for a young physician to assume that he needs to know little about drug therapy, and that he can depend almost totally upon the printed and word-of-mouth information submitted by pharmaceutical houses and their

detail men. He also is likely to consider that drug actions and dangers have been taken well into account in the manufacture and packaging of drugs, and that he needs only a perfunctory bit of information in order to prescribe properly. Though all of this is essentially true, and the practice of therapeutics has, in fact, been greatly simplified by these developments, it is equally true that the very wealth of drug products, drug names, and drug literature makes it essential that the young physician be taught some basis for judgment and selection. In this connection I strongly recommend a most pertinent article by Dr. David Barr (4), entitled "Hazards of Modern Diagnosis and Therapy—The Price We Pay," in which the difficulties are exemplified. In spite of the problems created, however, we must recognize that pharmaceutical manufacturing presents great advantages, and we must govern ourselves accordingly.

RECOMMENDATIONS FOR IMPROVEMENT

The end-result of the two principal elements discussed (and many other contributing factors undiscussed) is a current, but not necessarily basic, diminution of interest in therapeutics. How to stimulate interest, therefore, is the problem. As with any problem, there are several possible solutions. From my experience I should like to make the following suggestions for strengthening the teaching of therapeutics on the graduate level: 1) therapeutic conferences, 2) review of therapeutic failures, and 3) planned interjection of the subject in every teaching conference, every case discussion, and every ward round.

Therapeutic conference

The therapeutic conference is a most effective mechanism for review—one which can be scheduled independently or can be substituted at periodic intervals for Journal Clubs. In fact, therapy can be made the subject of the Journal Club itself, if semantics is a problem. The assignment of specific therapeutic subjects is basic. In the consideration of any drug, emphasis should be placed on chemical composition, mode and site of action, dosage, frequency of administration, rate of absorption, possible effective blood levels, biochemical tests for blood levels, rate and route of elimination, symptoms of idiosyncracies and overdosage, reactions, allergies, and contraindications. These points emphasize to the young physician that there is much more to prescribing a drug than the mere writing of its name and its dosage and the times of administration on a prescription blank or order book. Parallel study of a newly popularized agent and of an equivalent proven remedy multiplies the efficacy of the exercise by affording a basis of comparison. Everyone at the conference will benefit from the presentation and, if the leader be skillful, permanent interest may be engendered. However, it is the man who does the work and makes the presentation who really learns. Nothing fixes facts in the mind so firmly as work accomplished by oneself.

Review of failures

Review of therapeutic failures is another extremely effective teaching exercise —one which can and should be just as important as the studies of the Tissue

Committee, the reviews of pathologic findings, and the considerations of diagnoses and physical and laboratory findings. It is most revealing to analyze the whys and wherefores of therapeutic failures, to consider what could have been done better, to examine suggestions for correction of deficiencies either of omission or commission, and to highlight points for future guidance. Just as the autopsy is a teaching exercise of highest value, so the therapeutic review is a teaching exercise of equivalent importance in its own sphere.

Case discussion and conferences

To pursue this line of thought further I should like to make a suggestion. In graduate teaching programs we now have clinical-pathologic conferences and clinical-biochemical conferences, so why not have clinical-therapeutic conferences? It would seem that in the maintenance of interest by variety alone, an occasional CTC should be substituted for a CPC. Procedure can be strikingly similar. A particularly complicated case can be presented in all its details, the problems analyzed point by point, the diagnosis made, and appropriate methods of therapy outlined and discussed. As the concluding portion of the exercise, the instructor in therapeutics could close with a presentation of the actual therapy used in the case, point out the successes, the possible reasons for the failures, and the rationale of the measures taken. If time permits, comparison of the probable results of alternate regimens can lead to lively discussion. If the participants prepare for the exercises from previously distributed protocols and discussion is skillfully led, such an exercise can be a most profitable educational experience.

The interjection of therapeutics into every teaching conference and every case discussion should be a matter of prior planning and considered effort. Planned and repetitive emphasis has the effect not only of pointing out the importance of the subject, but of heightening and generating interest. It is in many ways comparable to a planned advertising campaign, and equally effective. Particularly on ward rounds, it is most efficacious to stop occasionally, question the medication ordered and ask the resident or intern writing the orders to point out the why, the wherefore, and the rationale of the therapy he is recommending. If this discussion is led into a detailed consideration of the properties of the drug, the student-physician cannot but have his attention focused and his interest aroused, if only by the necessity of being able to answer the instructor's question in ego-saving defense.

Short course in therapeutics

Strengthening postgraduate instruction in therapeutics requires different methods. Obviously, more time should be devoted to therapeutics in all of the courses presented. Not only should the subject be brought up more often in individual presentations, but hours or even sections of programs should be consigned to it. A particularly productive procedure is the one-day short course on recent trends and advances in therapy. If these were more generally presented, I am sure that a great many physicians would subscribe, their patients would

be benefited, and the enrollees would have the satisfaction of having acquired extremely useful information.

General campaign

As a parting thought, I should like to point out that in undergraduate education, workers in the fields of cancer, heart, and mental health must have been faced with this same problem of slackening interest at some past date, because at the present time the National Institutes of Health sponsor a Cancer Teaching Program, a Cardiovascular Teaching Program, and a Mental Disease Teaching Program in medical schools. Likewise, in undergraduate education the Department of Defense adroitly emphasizes military medicine, particularly the mass handling of casualties, through its program "Medical Education for National Defense." At the graduate level the American College of Surgeons aggressively sponsors interest in trauma, both individual and of mass casualty type, through its Trauma Committees. The Army Medical Service emphasizes its prime reason for existence—the handling of trauma, battlefield and otherwise—by a teaching campaign in its own graduate training program by two of the methods mentioned, *i.e.*, constant emphasis and interjection of the subject into all conferences and discussions, plus the holding of an annual area conference on trauma at each major teaching hospital. Perhaps then what therapeutics needs is a campaign in its behalf, perhaps a National Institute of Therapeutics to focus attention on the subject, to give financial support, and to co-ordinate activities in a manner parallel to those cited herein. Perhaps merely the passage of time will see the pendulum of interest swing back on its own merit. Whatever the method, may the renaissance be soon.

SUMMARY

The state into which the teaching of therapy has fallen in graduate and postgraduate medical education is pointed out. With the rapid strides made in the advancement of medicine in the past few years, emphasis has naturally been placed on diagnosis, physiologic-pathologic mechanisms, biochemistry and biologic developments. With this shift in emphasis, the teaching of therapy has markedly diminished in relative importance. In view of the dominant place that the practice of therapeutics has in the care of the patient, it would seem that a reshift in emphasis is in order.

A significant contributing factor to this adverse shift has been the decreasing necessity to understand drug actions, drug mechanisms and drug dangers, as a consequence of the development of the manufacturing pharmaceutical industry. Recognition of the fact that these developments are here to stay and must be taken into account in the reorientation toward therapy, will materially assist instruction in therapeutics to take its rightful place in the scheme of things.

Suggestions toward this end are made in the field of graduate and postgraduate instruction. In the graduate phase, periodic substitution of Therapeutic Journal Clubs for Journal Clubs per se, scheduled reviews of therapy failures, therapy conferences and seminars are in order. A conscious increase in the emphasis on

the therapeutic aspects of clinical instruction should also be made. In the postgraduate phase, courses in therapy during whole days, periods or hours should be included in courses on other subjects. The entire problem is one of emphasis. Publicity is needed, and perhaps even a drive should be sparked in this direction.

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DRUGS FOR THE IMPROVEMENT OF NEUROMUSCULAR COORDINATION*

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FIBROSITIS

The most common symptoms of a disabling nature in the field of rheumatic disease are the stiffness and aching which occur with inactivity—symptoms which are relieved by mild activity, salicylates and heat, but which recur with fatigue. In almost any textbook or paper describing one or more forms of arthritis these symptoms are included along with those caused by the joint lesion. It is true that stiffness and aching do occur with each of the rheumatic diseases, but they are not caused by the specific joint lesion in any form of arthritis. They are evidence of fibrositis, whether they exist alone or are secondary to the arthritic process. It is now apparent, although not generally accepted, that muscle atrophy caused by disuse, decreased use or prolonged strain accounts for these manifestations. Although the diagnosis of fibrositis has frequently been made by exclusion, it should be recognized immediately by its symptomatology. It is curable by rehabilitation of the atrophic muscles.

Fibrositis may exist alone as an acute or a chronic condition. In the acute phase, it is caused by the overuse of muscle that has been insufficiently trained or conditioned for the task required of it. The acute symptoms are generally short-lived, appearing within twenty-four to forty-eight hours after the excessive use. Almost everyone, unless absolutely inert in the past, has experienced this difficulty. It is possible for the acute phase to pass into the chronic stage, if inactivity as a protective measure is excessive. Unfortunately, rest of the painful, stiff area has been the general recommendation in the past, to such an extent, that most patients believe rest is essential. Present knowledge indicates that this is erroneous.

Chronic fibrositis is the type that often occurs secondarily in other rheumatic diseases. It is induced by protective measures undertaken when a joint is painful, such as limiting the motion, limping, and excessive rest. The traditional pattern of treatment, consisting of further protection and rest, increases the atrophy of the muscles involved and perpetuates the symptoms. A consideration of what influences or relieves symptoms of stiffness and aching and other pains readily differentiates fibrositis from the specific joint involvement. Stiffness and aching are associated with inactivity and are relieved by mild activity, whereas pain produced by an arthritis is present upon motion and use of the joint and is relieved by rest.

The treatment of fibrositis consists primarily of the use of salicylates and

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heat to relieve the aching pain. As the analgesic or heat becomes effective, the patient voluntarily begins to use the muscles to greater advantage and thus "limbers up" or "warms up" the stiff muscles. Rehabilitation is very slow, concomitant with the slightly increased use of the muscles permitted by the relief of aching afforded by analgesics. The need of a muscle-relaxing drug to relieve the stiffness has been recognized for some time.

MUSCLE RELAXANTS

The search for a preparation capable of inducing muscle relaxation in fibrositis led to the unfortunate acceptance of *prostigmine* without sufficient evidence of its effectiveness. The next preparation recommended for the treatment of fibrositis was *vitamin E* in large doses. This had a stimulating effect and seemed to be of some value but, again, it did not offer enough benefit.

A new era was initiated in 1947 when *mephenesin*[1] (Myanesin) was reported as having muscle-relaxing action by Berger and Bradley (1). Our experience with mephenesin was published in 1951 after more than a year of clinical evaluation (2). It proved to be the best preparation available up to that time for the relief of muscle spasm; 76.5 per cent of 200 patients were reported to be benefited from its use. It was necessary to give a morning dose consisting of 0.5 Gm. for every 46 pounds of body weight, followed by 0.5 to 0.75 Gm. every three hours thereafter. This dosage schedule caused relaxation of muscle spasm, which permitted more effective exercise and shortened the time required to overcome the muscular atrophy.

At this point a retraction of a statement made in our publication of 1951 is indicated. The statement was: "Supplemented by glutamic acid hydrochloride, mephenesin proved effective in many patients who otherwise failed to give the expected response. The daily dosage schedule for the acid where used, was 5 or 10 grains initially followed by 5 or 10 grains before lunch and dinner. Until this combination therapy has failed, mephenesin should not be discarded as ineffectual." Further experience with mephenesin, with and without glutamic acid or calcium glutamate, does not support this statement. The first mephenesin tablets available for clinical investigation were as hard as rocks and required additional acid to dissolve them. It was for this purpose that the glutamic acid was needed. It appeared from our data that the acid tended to enhance the rapidity and the degree of action of the mephenesin elixir and capsules. However, further experience has disproved this hypothesis.

Mephenesin was next administered in its *carbamate* form,[2] and there were reports of prolonged blood levels compared with those of mephenesin itself. In our experience, it did not prove any more effective than mephenesin. Following hard on the heels of these two preparations were a number of oral medications combining mephenesin with other constituents, all recommended as excellent

[1] Generic name for Myanesin. Provided for clinical investigation as Tolserol® by E. R. Squibb & Sons, New York, N. Y.

[2] Provided for clinical investigation as Tolseram® by E. R. Squibb & Sons, New York, N. Y.

muscle relaxants (Table 1). They vary considerably in their content of mephenesin, which is combined with such drugs as salicylates of one type or another, ascorbic acid, glutamic acid, or calcium glutamate. They also vary considerably in the dosage recommendations. We have had the opportunity to study many of these preparations prior to their commercial release, but none proved to have any greater effect than mephenesin or its carbamate. In fact, some of them were inferior. All of the remedies listed in Table 1 are currently available to the medical profession and apparently are being prescribed to a considerable degree or they would have been withdrawn from the market.

Not until meprobamate (June 1954) and zoxazolamine (February 1955) were presented to us for clinical investigation was any real forward step taken in the field of muscle-relaxing drugs.

TABLE 1

Muscle Relaxants—Available Oral Preparations (doses in mg.)

Name	Salicylate		Mephenesin			Barbital			Glutamate		Ascorbic Acid	Other	Dosage	
	Amide	Sodium		Carbamate	Paba	Buta-Na	Pheno-	Seco-	Ca	HCl			No. tablets or caps.	No. doses daily
Banesin	195		195			10							2	4–6
Expasmus	100		250									Dibenzyl succinate, 125 mg.	2	3 (12)
Haxsen			300					30					1	4
Kused			250				7.5		62.5			1-Hyoscyamine H Br 0.0625 mg.	2	3
Mephate			250							300			2	3–4
Mephosal		250	250										1–2	4–6
Neocyten		250			250						20	Physostigmine salicylate, .025 mg. homatropine methyl brom., 0.5 mg.	2	4
Myanil	125		250										2–4	3–4
Mybasal	195		195		195						10		2–8	4–6
Salimeph-C	250		250								30	Codeine, 1/8 gr.; colchicine, 1/260 gr.	2–3	4
Seconesin			400					30					1	4
Tolagesic	300		300										1–3	3–4
Tolseram				500									2–6	3–4
Tolseral			500										2–6	3–4
Tolyphy			500									Physostigmine salicylate, 0.35 mg.; atropine sulfate, 0.2 mg.	2	3–4

Meprobamate, 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate, is a derivative of a diol related to mephenesin. It was discovered in the Wallace Laboratories in 1950 by Ludwig and Piech (3). It is characterized by three pharmacologic properties—a muscle-relaxing action, an anti-convulsant action, and a taming effect (best seen in monkeys). It has a definite blocking action on interneurons, but does not effect any of the reflex arcs which contain no interneurons; this is the property which induces muscle relaxation. Another interesting property is its action upon the thalamus; electrical recordings show that in therapeutic doses there is a marked synchronizing of the activity, as indicated by the slowing of the frequency and a distinct increase in the voltage (4).

Zoxazolamine, 2-amino-5-chlorobenzoxazole, is most closely related to benzimidazole, which at one time was thought to have anti-viral activity. Zoxazolamine was developed and characterized by the research group of McNeil Laboratories. It induces a depression of the polysynaptic pathways (5). Clinical investigation of the influence of this drug on neuromuscular structures showed a central action with essentially no effect upon the muscle, myoneural junction, monosynaptic pathways or motor nerves. The pharmacologic action is relaxation of the spasm of striated muscles by means of depressing the central nervous system pathways and thus blocking the impulses causing the muscular spasm.

MEPROBAMATE AND ZOXAZOLAMINE

Method of administration

Meprobamate[3] was provided in a compressed, scored 400-mg. tablet. The dosage was 400 mg. three or four times a day, usually the latter. Zoxazolamine[4], for clinical investigation, was provided either in a 250-mg. tablet or a compressed, scored 500-mg. tablet. Later a 250-mg. enteric-coated tablet was available. The dosage was 250 or 500 mg. four times a day with the compressed tablet; if there was gastric irritation, the enteric-coated tablet was given in the same dosage. The enteric coating ("engestic coating") had an average disintegration time of three to four hours.

Selection of patients

For the purpose of comparing meprobamate and zoxazolamine, 96 patients were treated who had either fibrositis or one of the other rheumatic diseases with predominantly fibrositic symptoms (Table 2). It was not possible to have equal numbers of cases of each type of disease. Patients with the various conditions were included in the series as they presented themselves for treatment. Other conditions treated for screening purposes to determine whether or not these drugs might be effective were not included in this group; these were cases of lupus erythematosus, rheumatoid arthritis with rheumatoid spondylitis, subdeltoid bursitis and chronic gout.

[3] Provided for clinical investigation as Miltown® by Wallace Laboratories, New Brunswick, N. J.

[4] Provided for clinical investigation as Flexin® by McNeil Laboratories, Philadelphia, Pa.

TABLE 2

Comparison of Meprobamate and Zoxazolamine

Disease	No. of Patients		Patients Benefited			
			Mep.		Zox.	
	Mep.	Zox.	No.	Per cent	No.	Per cent
Rheumatoid spondylitis	21	16	19	90.4	15	93.7
Fibrositis	20	34	17	85.0	30	88.2
Cervical root syndrome	27	22	23	85.2	19	86.8
Rheumatoid arthritis mild	17	18	13	76.5	15	83.3
Torticollis, acute	4	2	4	100.0	2	100.0
Muscle spasm of the low back	3	3	3	100.0	3	100.0
Osteoarthritis of hip	4	1	4	100.0	1	100.0
	96	96				

Total benefit—meprobamate, 85.4 per cent; zoxazolamine, 88.5 per cent.

Response to therapy

The patients listed as having received benefit from these two drugs were: 1) those who had an excellent response, showing evidence of muscle relaxation within twenty to thirty minutes after the tablet was ingested and continuing to have good muscle relaxation throughout the day on a normal dosage schedule, and 2) those who had a good response, with only minimal stiffness or aching persisting beyond thirty to sixty minutes after taking the medication. The response was essentially the same to each drug. Over-all improvement occurred in 86.4 per cent of patients receiving meprobamate and in 88.5 per cent receiving zoxazolamine (Table 2).

All of the 17 patients (100 per cent) who had stiffness and aching associated with acute torticollis, muscle spasm of the low back or osteoarthritis of the hip were benefited. However, further experience with less careful selection of cases (*i.e.*, muscle spasm existing over a longer period of time, or osteoarthritis of the hip also producing symptoms) has proved that this 100 per cent response is greater than should be expected. In our study, these drugs were demonstrated to be superior to mephenesin preparations in rheumatoid spondylitis, fibrositis, cervical-root syndrome and mild rheumatoid arthritis. There was a longer duration of action (as shown by the efficacy of three or four doses per day) and a greater incidence of improvement.

Rheumatoid spondylitis (which is notorious for acute exacerbations and remissions of the joint lesions) becomes characterized after some months or years by chronic muscle spasm of the paravertebral muscles. It has been shown that these symptoms can be relieved to a considerable extent by vigorous physical therapy and posture training (6). The administration of muscle-relaxing drugs, even prior to the use of x-ray for the treatment of the specific joint condition, results in outstanding symptomatic relief. In this group of patients, 90.4 per cent receiving meprobamate and 93.7 per cent receiving zoxazolamine were improved (Table 2). Following roentgen therapy with 450–600 r to each of the

areas clinically and roentgenographically involved, the patients were able to exercise with greater ease, because the stiffness and aching were relieved by the continued use of these preparations. Both posture and motion improved in all patients who tolerated the drugs.

Fibrositis responded well to either drug. In these patients, the stiffness and aching was due to no other condition, and relief was rapidly evident following the ingestion of the medication. Although the total number of patients treated with each drug varies, the proportion showing improvement (85 and 88.2 per cent) was essentially the same (Table 2). The length of the "limbering-up" or "warming-up" period necessary after a night's rest or after any period of inactivity in excess of twenty to thirty minutes was considerably shortened when these drugs were administered. Rehabilitation exercises could be carried out as effectively in the early morning as later in the day when stiffness was relieved. The increased activity produced a rapid return of muscle tone and bulk. The morning improvement was even more marked if the medication could be taken about thirty to sixty minutes before arising; if some residual stiffness persisted on arising, it was rapidly dissipated by exercise.

Patients with cervical-root syndrome frequently had stiffness of the neck after periods of inactivity, which was gradually relieved by exercise or a "warming-up" period. This stiffness was caused by atrophy and spasm of the muscles of the cervical area following long periods of strain. Because of spasm, the vertebrae were forced closer together, with resulting pressure on the nerve roots. Of these patients, 85.2 per cent improved with meprobamate, and 86.8 per cent with zoxazolamine (Table 2). These drugs eased the pain but did not completely relieve it at first. Following relaxation of muscle spasm, however, it was possible to undertake rehabilitation exercises or the use of Sayre halter traction; with relief of the mechanical pressure on the fibers of the nerve roots, there was complete relief of pain.

In mild rheumatoid arthritis, when the specific joint lesions were not unduly troublesome, the response of the secondary aching pain and stiffness was fairly satisfactory. As may be seen in Table 2, there appeared to be approximately a 7 per cent difference between the effectiveness of meprobamate and that of zoxazolamine. This difference, however, was more apparent than real. Although the patients had been selected as having the same type of disease, several of those who received meprobamate eventually proved to have greater disability involving the affected joints than had been anticipated at the time they were given the medication. Therefore, to all intents and purposes the proportion of patients responding to the two drugs was essentially the same. The use of muscle-relaxing drugs in this type of rheumatoid arthritis illustrates an important point. With the relief of stiffness and aching, the incapacity of patients with mild joint involvement was almost completely eliminated. This would indicate that the disability and crippling effects of rheumatoid arthritis are more often due to the fibrositic involvement than to the actual joint lesions. The flexion deformities which are so common are due to imbalance, atrophy, spasm and shortening of the muscles, from prolonged protection of painful joints. If muscle tone can be kept normal or close to normal, deformities should be prevented. It is just as im-

portant, if not more so, to treat the fibrositic symptoms symptomatically in order to permit better rehabilitation as it is to treat the specific rheumatoid involvement. However, both can be treated beneficially at the same time. In the past, rheumatoid arthritis has been treated with such drugs as gold salts or salicylates, often with complete remission of the joint lesions. Nevertheless, some patients remained just as crippled as ever, because they failed to cooperate in the rehabilitation program to rebuild the muscles which had become atrophic because of discomfort and limited motion. A few patients will never cooperate, but in most instances a simple explanation of the pathology in the joints and muscles, when accompanied by demonstration of some relief of the disabling symptoms, will elicit good cooperation in a self-help program.

Toxic effects

The comparison of the toxic effects of meprobamate and zoxazolamine in our series of 192 patients is presented in Table 3. There were nine varieties of reaction with meprobamate therapy, and ten with zoxazolamine. Those most commonly seen with one drug were of a different nature from those seen with the other.

Meprobamate caused drowsiness in 48 patients. In 21 of these, this symptom was controlled upon continuation of the same dosage; and in 12, upon decreasing the dosage by 50 per cent; in only 15 was it necessary to discontinue the drug. The other most common side-effect was sluggishness of the bowel (8 patients), resembling that sometimes seen during salicylate or ferrous sulfate therapy. Slowing of the bowel activity was overcome in 6 patients by a reduction of the dosage, and required discontinuance of medication in 2. Each of the other toxic effects listed in Table 3 was in only 1 patient. Nausea disappeared when the dosage was reduced by 50 per cent. On the other hand, nausea and vomiting,

TABLE 3

Toxicity of Meprobamate and Zoxazolamine

Effect	No. of Side Effects		Cleared on Same Dose		Cleared on 50% Dose	
	Mep.	Zox.	Mep.	Zox.	Mep.	Zox.
Drowsiness	48	3	21	0	12	2
Nausea	1	12	0	3	1	7
Nausea and vomiting	1	0	0	—	0	—
Dizziness	0	11	—	4	—	5
Sluggish bowel	8	0	0	—	6	—
Epigastric burning	0	4	—	0	—	2
Light-headedness	0	5	—	2	—	3
Over-stimulation	1	4	0	0	0	2
Depression	0	1	—	0	—	0
Exhaustion	1	0	0	—	0	—
Ulcer symptoms	1	0	0	—	0	—
Rash	1	1	0	0	0	0
Chills and fever	0	1	—	0	—	0
Burning and tearing of eyes	0	1	—	0	—	0
	62	43	21	9	19	21

over-stimulation, exhaustion, ulcer symptoms and rash were considered severe enough for discontinuance of therapy; none of these side-effects persisted thereafter. In the patient who had a recurrence of ulcer symptoms, an anti-ulcer program was re-instituted for a week, and the patient with the rash received local hydrocortisone ointments for several days. None of the patients receiving meprobamate experienced dizziness, epigastric burning, light-headedness, depression, chills and fever, or burning and tearing of the eyes. To date, there has been no development of purpura hemorrhagica, as reported by Gottlieb (7).

In the patients receiving zoxazolamine, the most common findings were nausea, dizziness, light-headedness, epigastric burning, over-stimulation and drowsiness, in that order of frequency. Nausea occurred in 12 patients, but required discontinuance of therapy in only 2; it cleared with continuation of the same dosage in 3, and with halving of the dosage in 7. Mild dizziness cleared in 4 of 11 patients with no change in dosage; it was no longer a problem in 5 after the medication was decreased by 50 per cent, and required discontinuance in only 2. Of the 5 patients afflicted with light-headedness, 2 recovered without changing dosage, and 3 with decreased dosage. Epigastric burning and over-stimulation (8 patients) were severe enough to require discontinuance of medication in 2 instances, but these symptoms cleared in 2 other instances with lowered dosage. Depression, rash, chills and fever, and burning and tearing of the eyes occurred in 1 patient each; in all 4, these symptoms were considered severe enough to require omission of medication—whereupon they cleared rapidly. There were only 3 cases of drowsiness with zoxazolamine therapy; in 2, this symptom improved after decreasing the dosage, but in 1 it was severe enough to require discontinuance of therapy.

Comparison of the effects of these two medications show 62 instances of toxicity with meprobamate and 43 with zoxazolamine. However, meprobamate therapy was discontinued in only 22 patients, and zoxazolamine in only 13 patients. In this series, there was an incidence of 13.5 per cent toxicity for zoxazolamine and 23 per cent toxicity for meprobamate. In the latter instance, two thirds of the side-effects consisted of drowsiness, a symptom which has been found to be desirable in the treatment of many patients.

Choice of drug for clinical use

The question of preference has frequently been raised in discussions of these new muscle-relaxing preparations. In general, they are essentially equal in their effectiveness, but they lend themselves to paired action with a proper selection of patients. No patient, to date, has exhibited intolerance or refractoriness to both drugs.

The choice of which preparation to use in a given patient is dependent primarily upon the action of the drug and the tolerance of the patient. In general, the choices are as follows:

1. The tense, nervous, fearful, hyperactive type of rheumatic patient generally does well on meprobamate, 400 mg. four times a day.
2. The depressed, slow-moving, relatively inactive rheumatic patient responds better to zoxazolamine, 250 to 500 mg. four times a day.

3. Patients in the foregoing Group 2 who have difficulty in sleeping while receiving zoxazolamine four times a day, may have the dose frequency reduced to three times a day before or after meals, with meprobamate one or two tablets at bedtime.
4. If zoxazolamine causes over-stimulation, it may be better to give alternate doses of this drug and meprobamate, starting the day with the former and ending the day with the latter.
5. Patients, with or without rheumatic disease, who require intermittent or even fairly regular bedtime sedation respond well to meprobamate upon retiring. Some patients require only 400 mg., others 800 mg., for complete restful sleep. Many have volunteered the information that they no longer turn or toss in bed, but remain throughout the night in the position they first assumed on retiring, as indicated by the fact that there is no disturbance of the bedclothing on awakening in the morning. There is no hangover and the patient is well rested. When fibrositis is present, there may be some increased stiffness due to the inactivity during the night, but this is quickly relieved by the first morning dose of the muscle relaxant.
6. The use of either one of these newest preparations for the treatment of the symptoms of acute fibrositis (due to overuse of muscles) can prevent over-resting and the development of muscle atrophy and a chronic fibrositis. Medication for the acute phase is seldom needed longer than a few days to a week. At the same time patients should be encouraged to carry on their activities as normally as possible in order to prevent undue atrophy.

COMMENT

The discovery of mephenesin opened an entirely new approach to the therapy of the rheumatic diseases. Stemming from this discovery, great interest has been shown in finding better muscle-relaxing drugs which will not produce paralysis or weakness in the muscles relieved of spasm. This is only symptomatic therapy, but the patient is enabled to enter into a program of rehabilitation which can overcome the cause of stiffness and aching after inactivity. Unless a program of muscle rebuilding is instituted, symptomatic therapy will be required for long periods of time, with the possibility that the cause of the symptoms may never be completely overcome. Meprobamate and zoxazolamine, are the newest and best muscle relaxants for use in this type of therapy.

Fibrositis, tardily recognized in this country as a specific entity, is increasing by leaps and bounds due to the present mode of living. The trend is toward less and less physical activity by greater use of wheels. More and more drive-in facilities are available; one need no longer get out of one's car to go to the bank; there are golf-mobiles to take the tired golfer from tee to tee; entertainment is now possible at home by just seating oneself in front of a television screen for the entire evening. This increased inactivity is reflected in increased muscular atrophy with a production of fibrositis. To the layman, the first signs of fibrositis mean the need for more rest; this, in turn, results in more atrophy, an increase in symptoms, and prolongation of the discomfort. It has been recently

agreed by several outstanding football coaches and college trainers that ten years ago it was necessary to spend several weeks loosening up the well developed muscles of football players. Now it requires a month to build up these muscles in order to prevent injuries. One coach noted that, even when driving a car, athletes get even less exercise than before, since one no longer needs to press a clutch to shift gears. This is just another sign of the times. The gravity of poor muscular condition brought on by less and less physical activity should be realized by the medical profession and through them by the general public, unless this trend is to become disastrous.

In chronic fibrositis the patient must be impressed with the need for rehabilitation. He may be more convinced, if the necessity for muscle rebuilding is explained, and a demonstration is made of the muscle-relaxing effect of either meprobamate or zoxazolamine. When the sought-for effect occurs and stiffness is relieved as predicted, cooperation in a self-help program is almost assured.

It is most unfortunate that a stigma has been attached to meprobamate therapy by the incomplete reporting of its use in the lay literature (8, 9). Diagnoses of psychoneurosis are still in ill-repute with a large portion of the laity. When they read about a popular drug receiving plaudits for the relief of neurotic symptoms in the weekly news journals and newspaper columns, and hear it jokingly referred to by comedians, they gain the impression that it is of value only in these conditions. This opinion is so common that many patients have discontinued the medication and changed doctors because they thought they were being hoodwinked when the drug was prescribed for muscle relaxation. Judging from the beneficial effect of meprobamate in the field of rheumatic disease, it would appear that its most valuable property is that of muscle relaxation; this action, more than any other, brings about the relief of tension and the calming effect which is so popularly sought. This concept is further supported by the fact that zoxazolamine, which causes very little drowsiness, also relieves these people. Large numbers of people have never learned how to relax; now, for the first time, this occurs in their tense, tight muscles and consequently their tension states are eased.

It is hoped that the presentation and publication of information regarding the use of muscle-relaxing drugs will permit better understanding of their use and thus a better acceptance by patients without the stigma that is presently attached to them. Their action differs from that of the ataraxic or tranquilizing drugs. It is suggested that meprobamate and zoxazolamine are improperly classified as ataraxics. They would be more properly described as "lissive"[5] agents (10).

CONCLUSIONS

Meprobamate and zoxazolamine, though unrelated chemically, have the common property of inducing muscular relaxation. They are essentially equal in effectiveness, and complement rather than compete with each other. Some of the side-effects can be used to good advantage. For instance, the tendency to drowsiness induced by meprobamate may be used to slow down hyper-

[5] Inducing relaxation of excessive skeletal muscle tonus (spasm), without paralysis.

active patients. On the other hand, the lack of soporific effect following administration of zoxazolamine makes this drug useful in patients who tend to be depressed and inactive.

In our series of patients, there was no evidence of serious toxicity with either preparation. Approximately two thirds of the toxic effects which did occur could be overcome by cutting the dosage in half. Only activation of ulcer symptoms, rash, chills and fever, burning and tearing of the eyes, and depression were serious enough to cause immediate discontinuation of therapy.

Meprobamate and zoxazolamine do not fit properly into the classification of ataraxics, but are better described as "lissive" agents. They are the best muscle relaxants available at present. Therapy should be individualized, and the choice of one or the other drug should depend upon the type of patient to be treated. These preparations may be combined when desired, with no evidence of incompatibility.

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STUDIES WITH RADIOACTIVE DIGITALIS†*

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The cardiac glycosides have probably been investigated more extensively than any other group of drugs and we have a fairly complete and accurate picture of their circulatory effects. However, to date, the body of knowledge concerning the metabolic fate of digitalis in man is very limited. With the availability of isotopically labeled C^{14}-digitoxin it has been possible to overcome some of the difficulties encountered by earlier investigators in measuring microgram quantities or less of the cardiac glycoside in body tissue.

The purpose of this communication is to summarize our findings on the blood level, tissue distribution, excretion and placental transfer of radioactive digitoxin in human subjects.

METHOD

The radioactive digitoxin administered to the patients was prepared by biosynthesis using *Digitalis purpurea L.* plants exposed to an atmosphere of carbon-14 dioxide. The method of biosynthesis and isolation of the crystalline labeled glycoside has been reported earlier (1).

For the blood level and renal excretion studies, 8 patients with congestive heart failure of varying degrees of severity were selected. The 8 patients were divided into two equal groups, one group receiving 0.5 mg. of radioactive digitoxin and the other group receiving from 1.2 to 1.5 mg. Each group received a single intravenous dose of the labeled drug. Prior to the administration of C^{14}-digitoxin, digitalis preparations were withheld for fourteen to thirty-four days in order to permit the administration of a relatively large dose of digitoxin. Further digitalis therapy was discontinued for fourteen days or longer after administration of the labeled drug. Blood samples (10 to 20 ml.) were withdrawn by venipuncture at various time intervals up to ninety-six hours after injection of the drug. After withdrawal of each blood sample, the blood was quickly transferred into a heparinized tube and immediately stored at $-17°C$. Daily 24-hour urine samples were also collected for periods up to eighty days after administration of the labeled drug. All urine samples were lyophilized upon collection and stored as the dehydrated powder.

The tissue distribution study was conducted on 3 patients in whom the prognoses were poor. During the terminal stages multiple doses of radioactive digi-

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toxin were administered intravenously at varying intervals until a short time before death, in order to maintain adequate tissue concentrations of the drug. Patient E. W. received a total dose of 0.3 mg. up to five days before death, the last dose being administered sixteen hours before; Patient M. S. received a total of 0.6 mg. up to eleven days before death, the last dose being administered thirty-six hours before; and Patient T. K. received 1.0 mg. up to six days before death, the last dose being injected thirty-five hours before death occurred. Autopsies were performed within two hours after death and tissue samples were obtained at this time. In order to prevent *in vitro* degradation of the parent compound, all samples were immediately frozen with solid carbon dioxide and stored at −17°C.

Placental transfer studies were conducted on 3 pregnant women who required surgical expulsion of the fetus for various clinical reasons. A dose of 0.25 to 0.50 mg. of the labeled drug was injected 2.7 to 5.0 hours before removal of the fetus. The period of gestation for the 3 patients was 11 to 12 weeks. A fourth woman was also included in the study, whose fetus was diagnosed as an anencephalic monster. One-half mg. of C^{14}-digitoxin was administered approximately two to three hours before the expected time of delivery. However, the fetal heart beat stopped during delivery, two hours after injection of the labeled glycoside. The still birth occurred during the thirty-fourth week of gestation. Various fetal organs were removed, thoroughly washed with isotonic saline and stored at −17°C. Maternal blood samples (both immediately before administration of the radioactive drug and after removal of the fetus) as well as samples of maternal uterine muscle were obtained.

The isolation of unchanged digitoxin and the fractionation of its metabolic products from tissues and body fluids have been presented earlier in publications (2–5) dealing with the individual aspects of the various studies being considered in the present communication. The isotope dilution technique of adding non-labeled carrier digitoxin to the extraction mixture was utilized to aid in the isolation of micro amounts of the labeled glycoside. Isolation and fractionation of the labeled compounds was effected by using both solvent-solvent extraction and chromatographic separation. All the radioactivity in the various fractions other than that of the unchanged drug were combined and considered to represent radioactivity from metabolic products of the parent compound. Radioassay of the various extracted fractions, except the original tissue residue from the homogenate fraction were made using an internal gas-flow Geiger counter. The tissue residue was combusted to carbon dioxide in a vacuum combustion line and counted in an ionization chamber, using a vibrating reed electrometer according to the method of Brownell and Luckhardt (6).

RESULTS AND DISCUSSION

Blood levels

Blood level determinations for both the unchanged drug and its metabolic products indicate that labeled compounds can be detected in human blood as long as ninety-six hours after its intravenous administration. As shown by the

curves in Figure 1, approximately 42 per cent of the injected dose can be detected in the vascular system as unchanged digitoxin within two minutes after administration of 0.5 mg. or 1.2 to 1.5 mg. of the labeled glycoside. At the end of fifteen minutes the proportion is approximately 12 per cent, after one hour 6 per cent, after six hours 3 per cent, after twenty-four hours 2 per cent, and after ninety-six hours trace amounts up to 1 per cent. It will be noted from the curves representing total C^{14}, which includes both the parent compound and metabolites, that there is a higher percentage of metabolic products in the blood than of the unchanged drug.

Figure 2 represents the semi-logarithmic plot of the concentration of unchanged digitoxin expressed as micrograms (μg.) per 100 ml. of blood. If we assume that this plot is the resultant of first-order or quasi–first-order reactions, the curve can be resolved into two straight-line components from which it is possible to determine the biologic half-life of the two components (7, 8). As shown in Figure 2, the biologic half-life of the first component is fifteen to thirty minutes, and that of the second component is forty-eight to fifty-four hours. Comparison of the biologic half-lives of digitoxin between the two doses studied suggests that the rate of disappearance for the vascular system is not dose-dependent.

Tissue distribution of digitoxin in terminal patients

Considering the specific effect of digitoxin upon the heart, many of the earlier investigators postulated that the cardiac glycosides had a selective affinity for the myocardial tissue. Our findings (Figs. 3 and 4) indicate that the myocardium

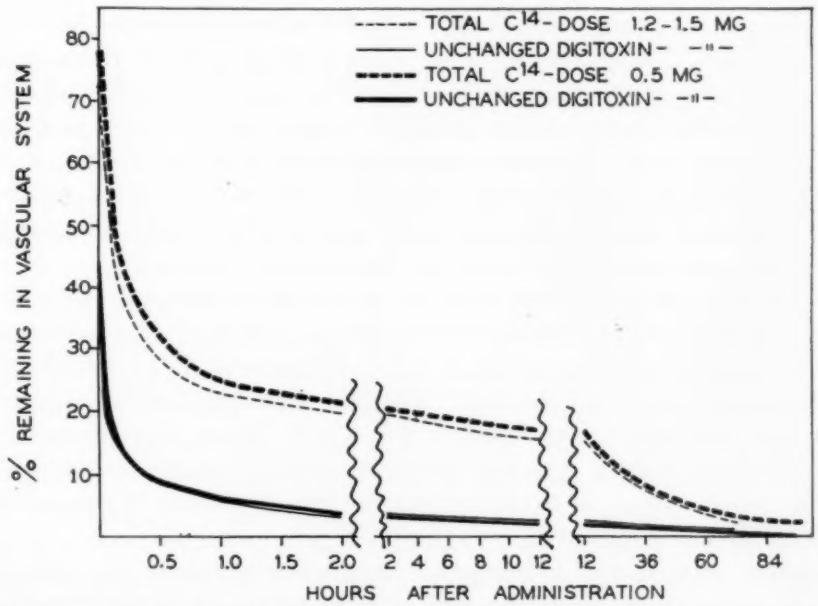

FIG. 1. Blood level curves showing percentage of dose remaining in vascular system as unchanged digitoxin and total C^{14} after a single intravenous administration of radioactive digitoxin.

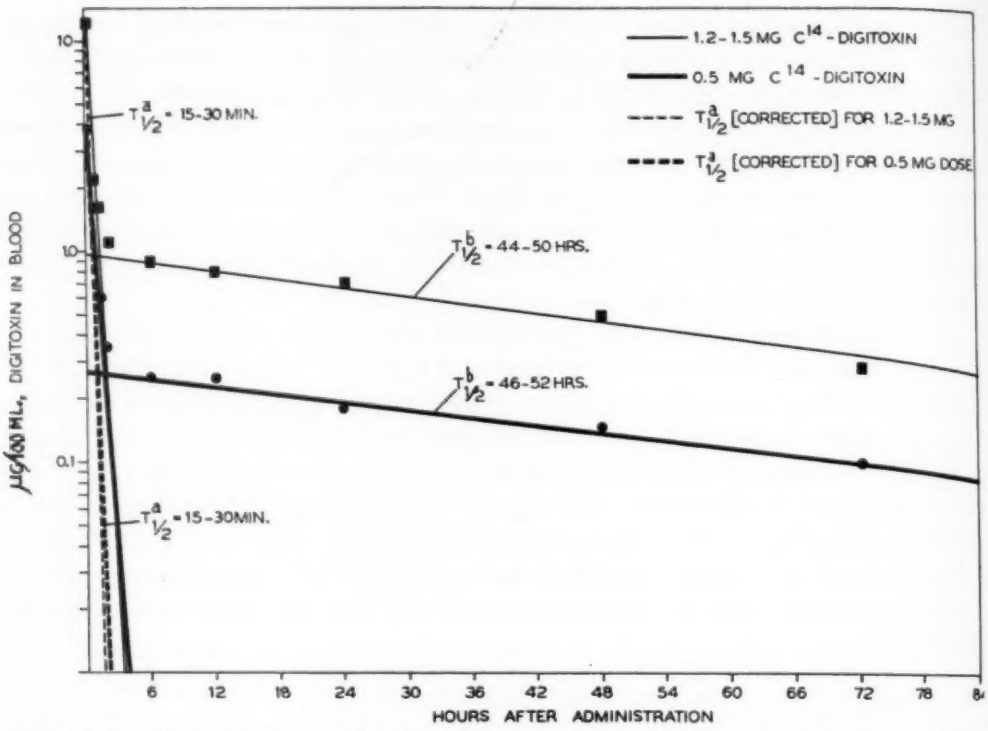

FIG. 2. Semi-logarithmic plot showing disappearance rate of unchanged digitoxin in blood after intravenous administration of C^{14}-digitoxin.

has no greater affinity for digitoxin than has any other organ. On a tissue-weight basis, the highest concentration of unchanged digitoxin was found in the colonic contents—4.6 to 13.0 μg. per 100 Gm. This was followed by the gall-bladder contents, jejunal contents, kidney, ileal contents, lung, liver, jejunum, ventricle and auricle—0.6 to 3.7 μg. per 100 Gm. The concentration in the blood was very low in comparison with the organs mentioned, and there was only a trace or no detectable amount in skeletal muscle. The high concentration noted in the colonic contents is believed to be a reflection of the process of concentration which takes place through reabsorption of water by the colonic mucosa.

When the amount of the drug found in the tissues is expressed in terms of the percentage of the total administered dose (Fig. 4), the liver was found to contain the largest amount of unchanged drug (1.5 to 2.8 per cent). This was followed by the colonic contents, kidney, blood, ventricle, jejunum, jejunal contents and ileum. Lesser quantities were found in the other organs. It is believed that an appreciable amount of the glycoside is also stored in the skeletal muscle, but due to the low concentration of the drug, quantitative determinations could not be made.

It is worthy of note that in almost all organs studied there was a higher concentration of metabolic products than of the unchanged drug. By calculating the metabolite:digitoxin ratio for each of the organs, it is possible to obtain information on the organs involved in metabolic conversion of digitoxin. The tissues

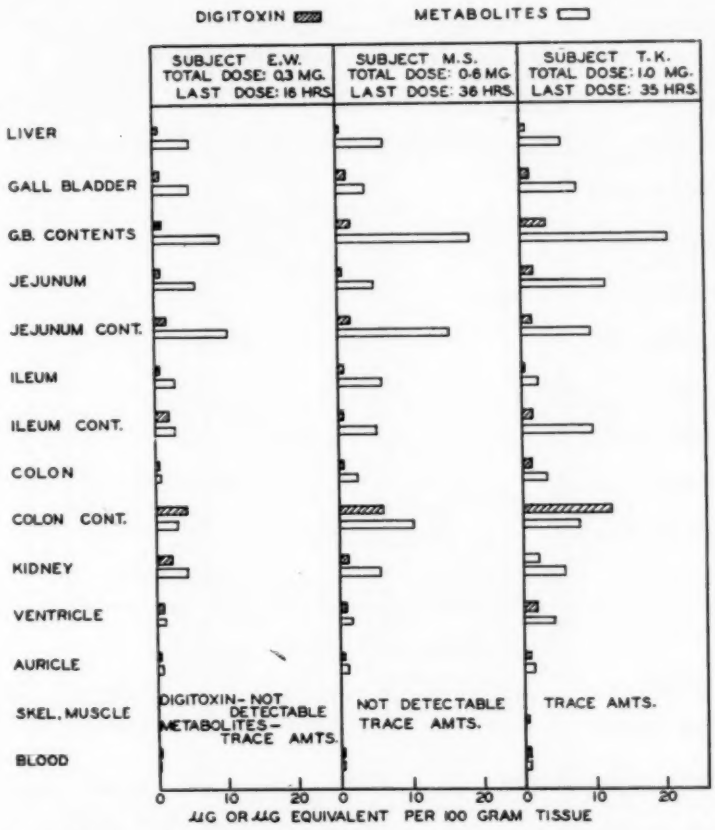

FIG. 3. Tissue distribution of radioactive digitoxin in human organs.

with the highest ratios were the spleen with an average ratio of 16, liver 9, contents of gall-bladder and jejunum 7, ileal contents 5, colonic contents 1, kidney 3, lung and ventricle 2, and blood 4. The high ratio for the spleen is difficult to explain, since the spleen is not considered to be an important detoxifying organ; however, it may have been due to accumulation of metabolite-protein complexes by the reticulo-endothelial cells. In all probability the high ratio observed in the liver indicates that this may be the major organ of detoxification. The relatively high ratios for the contents of the gall-bladder and small intestine may reflect the movement of digitoxin and its metabolic products from the liver without further degradation of the parent compound. However, it is not possible to rule out metabolic conversion of the drug in the intestinal mucosa. The ratio may not have risen significantly above the liver ratio due to the fact that reabsorption of metabolites by the small intestine was proceeding at a more rapid rate than for the unchanged drug.

The entero-hepatic cycling of digitoxin and its metabolites is indicated by the passage of labeled compounds into the small intestine by way of the biliary tract and their reabsorption by the intestinal mucosa. Reabsorption of both digitoxin and its metabolites during its passage through the small intestine is shown by the lower concentration of these labeled compounds in the ileum and

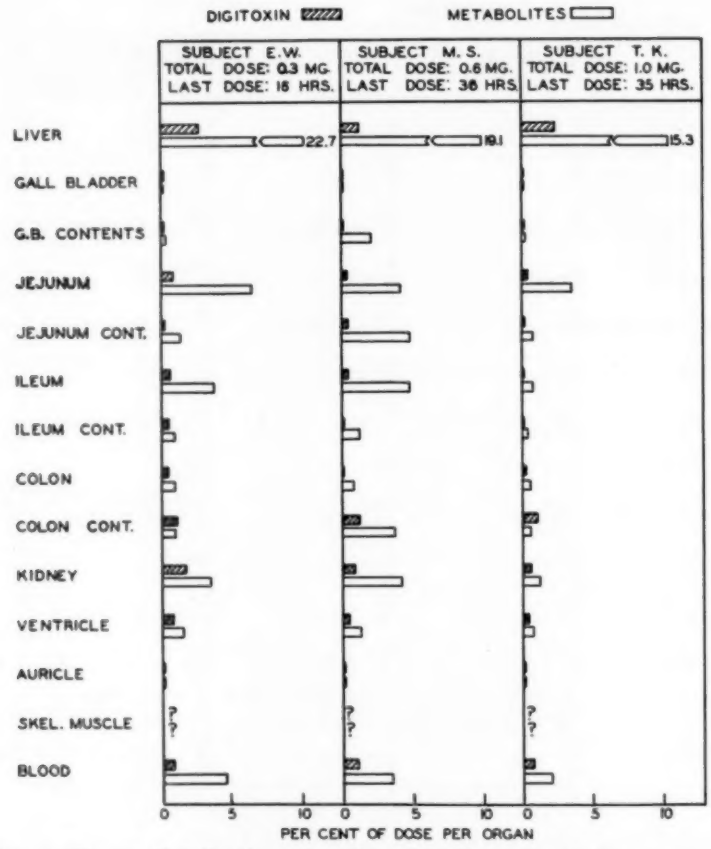

FIG. 4. Tissue distribution of radioactive digitoxin in human organs.

ileal contents as compared with that in the jejunum and jejunal contents. It is also of interest that in the small intestine the rate of reabsorption of metabolites was greater than that of unchanged digitoxin, as suggested by the decrease in the metabolite:digitoxin ratio during passage of labeled products from the small to the large intestine.

Excretion

The average daily renal excretion rates of the labeled compounds for the 4 patients who received a 0.5 mg. of radioactive digitoxin intravenously is shown in Figure 5. A similar graph for the 4 patients who received from 1.2 to 1.5 mg. is shown in Figure 6. As illustrated by the curves, there was a rapid initial decline in the amount of labeled compounds eliminated daily, followed by a gradual leveling off of excretion. During the initial three-day period, 20 per cent of the administered dose was eliminated as total carbon-14, and about half of this amount was excreted during the first twenty-four hours.

Comparison of the amounts of drug excreted daily following the two doses demonstrates that the excretion rate is dependent upon the amount in the body. The average amounts of unchanged digitoxin excreted in the urine during the

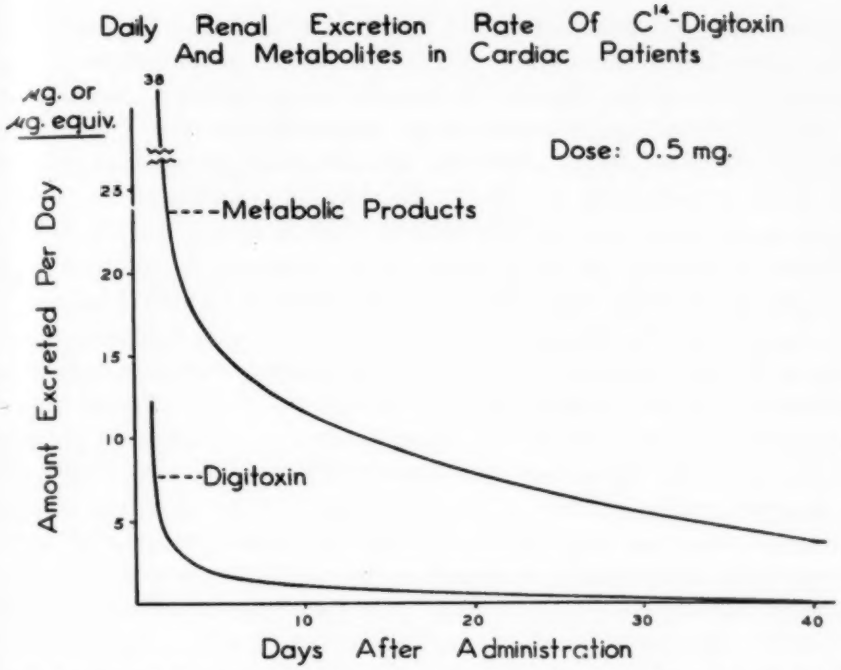

FIG. 5. Average daily renal excretion rate of unchanged digitoxin and its metabolic products in 4 cardiac patients receiving C^{14}-digitoxin (dose, 0.5 mg. intravenously).

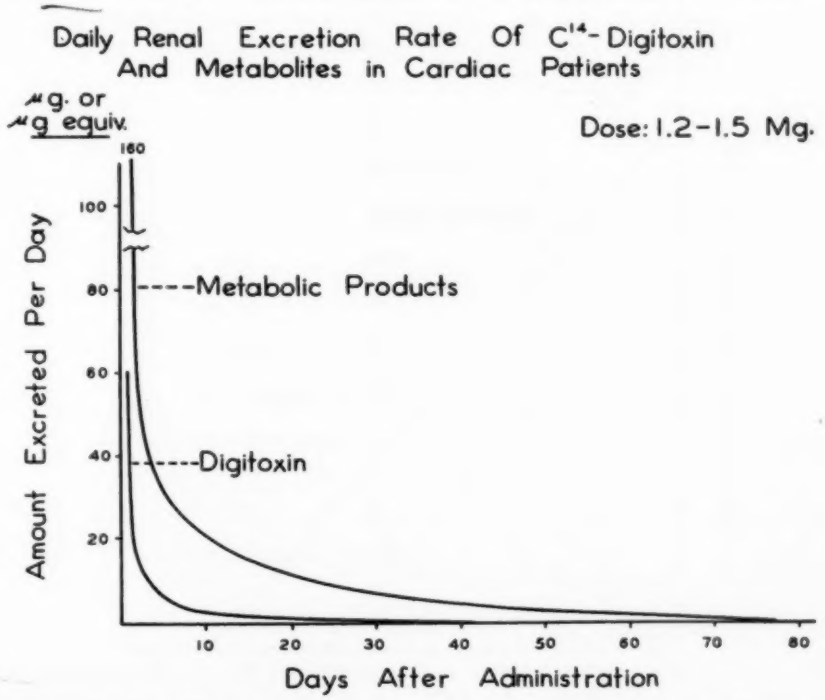

FIG. 6. Average daily renal excretion rate of unchanged digitoxin and its metabolic products in 4 cardiac patients receiving C^{14}-digitoxin (dose, 1.2 to 1.5 mg. intravenously).

first, second, fifth, twelfth and twenty-third days after administration of 0.5 mg. of the labeled drug were 13.0, 3.0, 2.0, 0.7 and 0.2 μg., respectively. For the corresponding days during the 1.2–1.5 mg. the dosage period, the amounts excreted were 61.0, 14.0, 4.0, 3.5 and 1.0 μg., respectively.

Results shown in Figures 5 and 6 also indicate that the injected glycoside is excreted over a considerable period of time. Minute amounts of the unchanged drug could be detected from twenty-three to fifty days after administration of the glycoside, depending upon the dosage used. Metabolic products of digitoxin were assayed in the urine from thirty-one to eighty days after administration.

A semi-log plot of the disappearance curve of unchanged digitoxin in urine is illustrated in Figure 7. Graphic calculation of the exponential rate constant indicates a biologic half-life of approximately nine days. This is in good agreement with the known clinical evidence for the long cumulative action of digitoxin.

Another significant finding was the demonstration that most of the administered drug was converted into metabolic products. Approximately 71 per cent of the original dose was excreted in the urine as metabolites of digitoxin, and only about 8 per cent could be detected as the parent compound.

Daily fecal samples were also obtained over a period of fourteen days from 2 of the patients who participated in the renal excretion study. Approximately 9 per cent of the original dose was excreted as unchanged digitoxin and 8 per cent

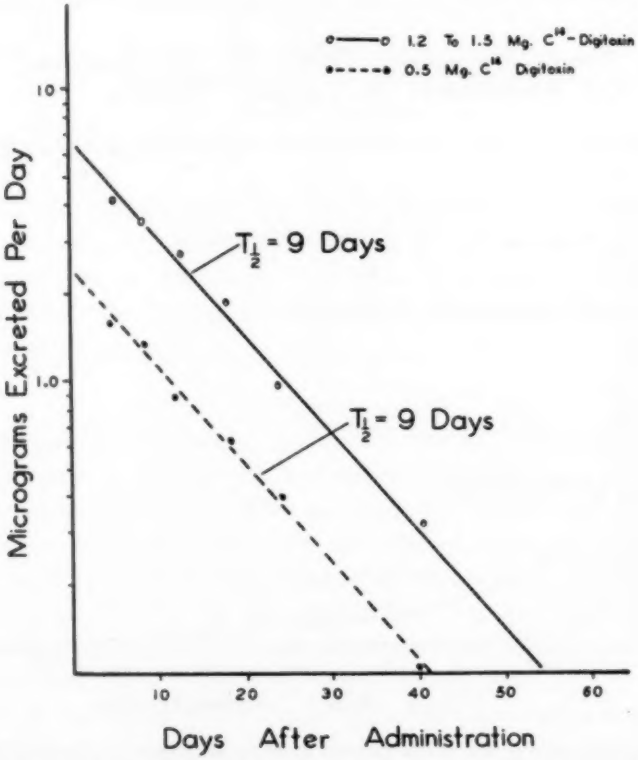

FIG. 7. Semi-logarithmic plot showing disappearance rate of unchanged digitoxin in urine after intravenous administration of C^{14}-digitoxin.

as metabolic products. Since 60 to 80 per cent of an administered dose of digitoxin is excreted by the urine in both the unchanged and metabolic form, the main organ involved in the ultimate elimination of digitoxin plus its metabolic products is the kidney. However, if only the unchanged drug is considered, the amount excreted in the urine is approximately the same as that excreted in the feces.

Placental transfer of digitoxin in pregnant women

Studies have also been conducted to investigate the passage of labeled digitoxin across the placental barrier of pregnant women and to determine the relative concentrations of labeled compounds in the various fetal organs.

Quantitative studies indicate that a small amount of the cardiac glycoside does cross the placental barrier as shown by its presence in the fetus between 1.7 to 5.0 hours after intravenous injection of the labeled drug into the mother. Less than 0.1 per cent of the injected dose was found as unchanged digitoxin, and less than 0.33 per cent as its metabolic products in the aborted fetuses of 11 to 12 weeks' gestation. In the near-term fetus, 0.84 per cent appeared as the unchanged drug and 3.49 per cent as metabolic products. This difference may be attributable to the increase in size of the near-term fetus, since there was no significant increase in the concentration on a tissue-weight basis.

The distribution of labeled digitoxin and its metabolic products in the various

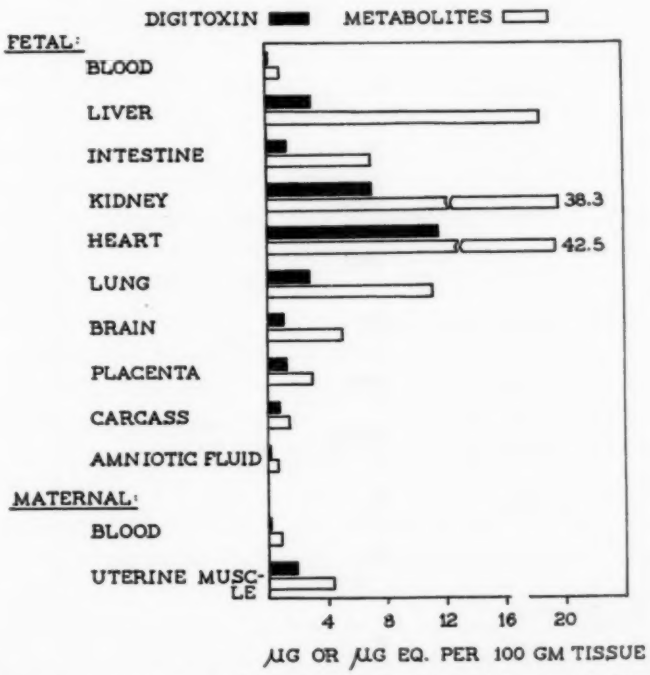

FIG. 8. Average concentration of radioactive digitoxin and its metabolites in organs from 3 human fetuses at 11 to 12 weeks of gestation, based on a dose of 0.5 mg. of labeled digitoxin administered intravenously to the mother 2.8 to 5.0 hours before therapeutic abortion. (One of the 3 mothers received a dose of only 0.25 mg. of labeled digitoxin, but the fetal values were corrected for a 0.5-mg. dose.)

organs of 11 to 12 week fetuses is shown in Figure 8. The fetal heart and kidney had relatively higher concentrations of the labeled drug and its metabolites than the other organs that were studied. In all organs there was a higher concentration of the metabolic products than of the parent compound. The presence of metabolites in the fetal tissues suggests either a metabolic conversion of the cardiac glycoside by the fetal tissues or passage of the metabolites across the placental barrier, or perhaps both. The high metabolite-to-digitoxin ratio noted in the fetal liver may be an indication that drug detoxification is already occurring in the liver by the eleventh week of gestation. The passage of digitoxin across the blood-brain barrier correlates well with the known effects of digitalis on the central nervous system.

The concentrations of digitoxin and its metabolites in the organs of the near-term fetus are shown in Figure 9. The concentrations of drug and metabolites in the organs selected for study were lower in general than those found in the organs of the 11 to 12 week fetuses. Part of this difference may be accounted for if the concentration of the drug is expressed in terms of its distribution per cell, since fetal cells are smaller in size during the eleventh and twelfth week of gestation than during the terminal stages of pregnancy. It is of interest that the biliary excretion of digitoxin and its metabolites could be demonstrated in the near-term fetus by the presence of these compounds in the liver, gall-bladder, and intestine.

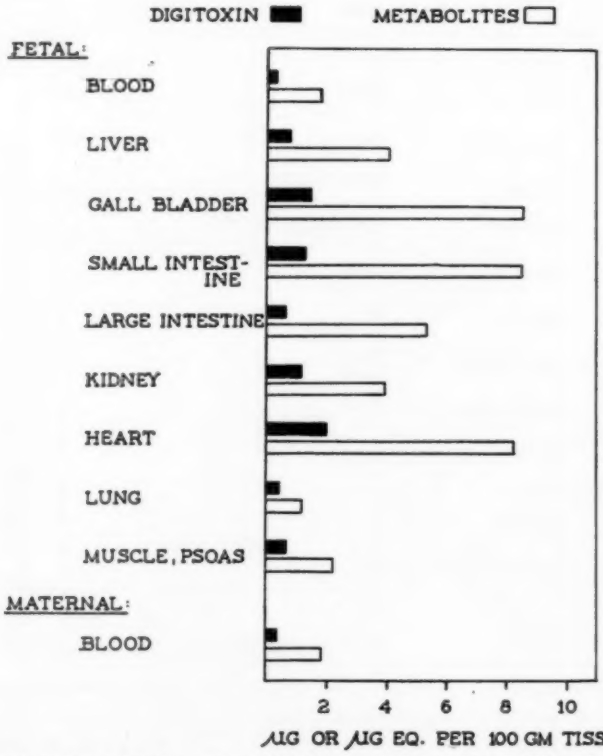

FIG. 9. Concentration of radioactive digitoxin and its metabolites in human fetal organs at 34 weeks of gestation. A dose of 0.5 mg. of labeled C^{14}-digitoxin was administered intravenously to the mother 1.7 hours before death that occurred during delivery.

A direct comparison of the concentration of digitoxin in the maternal heart with that in the fetal heart would have been very informative. However, since this was not possible, a sample of auricular appendage was obtained from a patient undergoing cardiac surgery who had received an injection of 0.5 mg. of C^{14}-digitoxin three hours before removal of the tissue. A comparison of the concentration of the unchanged drug in the heart of the near-term fetus with that in the adult auricular appendage indicates that in the fetus the concentration was approximately twice that in the adult. The concentration in the heart of the 11 to 12 week fetuses was approximately ten times greater. Here again the difference may possibly be explained on the basis of differences in cell size. Wollenberger (9) has postulated that mature and immature cells may have roughly the same number of drug-molecules per cell, although they differ on a tissue-weight basis, thus accounting for his finding that the heart of immature experimental animals is able to tolerate a larger dose of ouabain on a milligram-per-kilogram basis than is the heart of mature animals.

If Wollenberger's findings can be extrapolated to human beings, it seems likely that the minute amount of digitoxin (less than 1 per cent) that crosses the human placenta may be considered nontoxic to the unborn child.

SUMMARY

1. Using the isotope tracer technique, a quantitative study was made of the blood level, tissue distribution, excretion, and placental transfer of intravenously administered C^{14}-digitoxin in human subjects.

2. Blood level studies indicate that two exponential rate components can be calculated for the disappearance rate of unchanged digitoxin from the vascular system. The fast component has a biologic half-life of fifteen to thirty minutes, whereas the slower component has a half-life of forty-eight to fifty-four hours. It is believed that a third component, representing the disappearance rate of "firmly" bound digitoxin with a longer half-life, can be demonstrated if the blood concentration is followed for a longer period.

3. Tissue distribution studies in terminal patients demonstrated that cardiac tissue has no preferential affinity for the glycoside, as has been postulated by many earlier investigators. On a tissue-weight basis the kidney, and the contents of the gall-bladder, jejunum, ileum and colon had the highest concentration of the unchanged drug. Most of the administered glycoside was metabolized in the body, the liver being the main organ involved in the detoxification.

4. Renal excretion data showed that approximately 71 per cent of the dose was excreted in the urine as metabolites of digitoxin, and only about 8 per cent as the parent compound. Fecal excretion studies showed that approximately 9 per cent was eliminated as the unchanged drug and 8 per cent as metabolic products. The biologic half-life of the unchanged glycoside in urine was found to be nine days, which confirms the well known cumulative action of digitoxin observed clinically.

5. In placental transfer experiments, less than 1 per cent of the unchanged drug and less than 3.5 per cent of the metabolites could be detected in the fetus between 1.7 and 5.0 hours after injection of the labeled drug into the mother.

Acknowledgment

This communication includes data from various studies carried out earlier by the joint efforts of other colleagues. These include Drs. E. M. K. Geiling, P. J. Talso, F. E. Kelsey, E. J. Plotz, M. E. Davis, and Messrs. J. H. Curry, Jr. and F. D. Smith, Jr., to whom the author wishes to express his indebtedness and gratitude. The author also wishes to acknowledge appreciation to Drs. W. H. Adams and E. B. Bay for their cooperation in providing cardiac patients for this study, to Dr. R. W. Wissler for conducting the autopsies, and to Dr. E. Mika for growing the radioactive *Digitalis purpurea L.* plants from which the labeled C^{14}-digitoxin was obtained.

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PRESENT STATUS OF VIRAL VACCINES*

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One would assume from recent discussions and writings that viral vaccines had been developed entirely within the past decade and that even the term "virus" is new. Of course, both assumptions are false; the word "virus" is quite old and the first viral vaccine was developed centuries ago. This preparation was the "live" viral vaccine used in the procedure of "variolation" or intentional inoculation of persons with material from patients with smallpox. It was used in the Orient and Middle East since before the Christian era but was apparently first employed in Western Europe during the 18th Century. That a method which is so dangerous for both the vaccinee and the community at large was used at all attests to the fear and horror with which smallpox was viewed by the people of that era.

VACCINES

Smallpox

Variolation was replaced by vaccination, beginning shortly after the well known experiments of Jenner in the later years of the 18th Century. His experiments gave a solid experimental base to all subsequent work with attenuated vaccines. Great as Jenner's contributions were, we now realize that vaccination against smallpox is not perfect. Cases of generalized vaccinia occur in the ratio of 1 to 20,000 or 40,000 vaccinations; post-vaccinal encephalomyelitis occurs in Holland about once in 5,000 vaccinations and in Great Britain about once in 100,000 vaccinations. The incidence in the United States was thought to be lower, but in New York City where 5 million people were vaccinated in 1947, the ratio was 1 to 110,000 vaccinations; most cases fortunately, were mild. It has also been learned, contrary to our earlier ideas, that smallpox vaccination does not confer complete or permanent immunity. Studies in our Armed Forces and those of the British have shown that it is necessary to produce a very high degree of immunity if the individual is to withstand exposure to the severe type of smallpox found in Asia, the Middle East and North Africa. Apparently, this degree of immunity can be brought about with the present vaccine only by causing an actual infection with the living agent in the vaccine. This original immunity must then be bolstered by adequate, periodic revaccinations with highly potent vaccines given by an approved technique. I have spent a little

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time on these points because smallpox vaccine has been considered to be the model of a viral vaccine.

Rabies

Nearly a hundred years after Jenner's discovery Pasteur made the first attempts at vaccination against another human disease when he injected into a boy, who had been severely bitten by a rabid dog, a vaccine he had prepared, first by passage through rabbits until it was "fixed" for that species, and then by exposure to a differential desiccation process. The results were widely heralded at the time, and for about fifty years afterward it was assumed that rabies vaccine was highly effective. Then, about twenty years ago the value of vaccination against rabies began to be questioned and within the past decade we have even heard statements that rabies vaccine causes more deaths than rabies itself. Although it is unfortunately true that the incidence of post-rabic vaccine encephalomyelitis is higher than any of us like to see, and that vaccine has sometimes been given needlessly and has thus contributed to the incidence of such accidents, there are reasons for believing that this vaccine has value. By "this vaccine," I refer to the modern descendants of Pasteur's vaccine, such as the vaccines made by killing the rabies virus with chemicals or with ultraviolet irradiation. With the best of these it is possible to produce immunity in animals vaccinated after they have been exposed by inoculation with virus in a manner similar to natural exposure. Thus, a solid base exists for expecting immunity to develop in man under similar circumstances, especially in view of the fact that the incubation period is usually longer in man than in animals which are artificially exposed.

A review of the experience in Illinois indicates that the occasional human case of rabies that is reported practically always occurs in a person who failed for some reason to be vaccinated following exposure. At an earlier date, twenty years or more ago, there was an occasional instance in which the vaccine seemed not to have been protective. However, at that time there were no tests or standards of antigenicity and the vaccines then employed were probably, as Webster (1) showed, of very poor antigenicity. There are still some vaccine failures but practically all of these occur in persons who have been severely exposed and in whom the disease develops after a very short incubation period. In these cases the clinical disease is initiated long before antibodies are present in adequate titer in the blood stream. For that reason hyperimmune rabies serum is now being used in conjunction with rabies vaccine in severely exposed persons.

Since human rabies is a rare disease in the Western World, it is necessary to go to India for figures on the effectiveness of rabies vaccine. The 1954 Report of the Pasteur Institute of Southern India lists the following fatality rates for persons bitten by animals proved to be infectious because a bitten person or animal became rabid: among 207 completely treated with phenolized vaccine, 7.7 per cent; and among 71 not treated, 49.3 per cent. For persons bitten by the same animal, some vaccinated, others not, the report for 1954 furnishes the following figures:

Biting Animal	Deaths Among Completely Treated Persons	Deaths Among Untreated Persons
Jackal	0/12	5/23
Jackal	1/5	4/7
Dog	0/19	1/1
Dog	0/6	1/1
Dog	0/2	3/10

A word should be injected here in regard to the possible use in man of the recently developed attenuated virus vaccine propagated in chick embryos, the so-called Flury strain vaccine. This is apparently very effective for canine vaccination but it is not known whether it is safe and effective enough to be used in man. The studies of Schwab *et al.* (2) indicated that the antibody titers it produced in man were not as good as those produced with a Harris type commercial vaccine.

Methodology

From the advent of rabies vaccine to the introduction of the next group of viral vaccines, there was a long pause and for very good reasons. The disease agents of most of the other important viral infections, with one or two exceptions, had not been isolated and identified. There was a dearth of trained investigators, and methods for isolating and studying viruses were imperfectly developed. During this hiatus the viruses of yellow fever and poliomyelitis were isolated. More important, perhaps, was the growth in the field of methodology and, in particular, the discovery of the chick embryo as a tool for propagating and studying viruses. It is true that the viruses of *poliomyelitis*, *yellow fever* and *influenza* were all isolated and identified in animals. No vaccine against poliomyelitis could be developed, however, because monkeys were the only animal known to be susceptible to the virus, and infected monkey brain and spinal cord were not satisfactory sources of virus for vaccine production.

Vaccines for *yellow fever* have been produced from virus grown in animals but the one that has proved to be best was produced by passages of the virus in chick embryos after it had been passed through the brains of mice. The attenuated virus, which is the vaccine, is propagated in the chick embryo. Yellow fever vaccine is undoubtedly effective, as shown by experience in the field and in the vaccination of laboratory workers who often became infected before vaccine was available. However, the studies of Fox and his associates (3) have brought to light two facts of great interest: 1) the duration of immunity (judged by antibody levels) following use of this live virus vaccine is apparently not lifelong but probably lasts for several years; in children post-vaccination immunity probably persists for even shorter periods of time; and 2) following the use of some lots of vaccine about 0.5 per cent of the vaccinees experienced severe reactions, associated with encephalitis in about two thirds of the cases.

Influenza vaccine is also made by growing the virus strains in chick embryos; in this procedure, however, the virus is killed with formalin or ultraviolet light. Early results with influenza vaccine in controlled studies were very good, but

later the value of this vaccine was questioned. Recently, it has been found that apparent failures with influenza vaccine have been due to influenza-like infections with other viruses such as members of the APC group and, to a lesser extent, to introduction of new strains of the influenza virus itself, antigens for which have not been incorporated in the vaccine. Immunity is apparently short, probably not because influenza vaccine is of the "killed" type but because an attack of the disease seems to confer a short-lived immunity and vaccine cannot be expected to do better than that. In spite of this limitation, influenza vaccine seems to have achieved a place in therapeutics, especially in routine vaccination of military personnel, of those with debilitating diseases, and of those in the older age groups.

Among other vaccines propagated in the chick embryo which have been shown to have some value in controlled experiments or in limited use in the field are those against *equine encephalomyelitis*, *Japanese B encephalitis*, *dengue fever*, *mumps* and *Colorado tick fever*. All of these have restricted spheres of usefulness, such as in special groups in the Armed Forces, those exposed in certain areas, or in special population groups in which there are unusual risks, *e.g.*, persons engaged in manufacturing vaccines.

Attempts were made during that era to produce other vaccines from viruses grown in chick embryos. It was soon found that not all viruses could be adapted to the egg. Even when a virus was adapted and could be grown in this medium, it was not always possible to attentuate it or to inactivate it in such a way that a vaccine resulted. Measles may be cited as an example of apparent failure. Many unsuccessful attempts were made to adapt polio virus to the embryonated egg before 1953, when Cox and his colleagues (4) succeeded in doing so with the Lansing strain Type 2, by more than 150 serial passages in hamsters followed by serial passages in the egg. Since this feat was accomplished, Cox and his associates have apparently been able to adapt both of the other known types of poliomyelitis virus to the egg and are attempting to produce a human vaccine, probably of the "live" virus type.

Poliomyelitis

Except for developments such as this, efforts to produce other viral vaccines remained in the doldrums. For example, in the case of poliomyelitis, repeated attempts (some in our own laboratory) to grow virus in quantity and with high titer in the brain of an animal and to purify and concentrate it had failed. A large number of investigators had shown that it is possible to immunize mice or monkeys with living or killed virus in the form of monkey-cord preparations but the number of inoculations needed and the risks involved made it impractical to try these products in the human host even if there had been a sufficient supply of virus.

Obviously, what was needed was an abundant, cheap source of virus of high titer and relatively free from tissue. This became available through the brilliant studies of Enders, Weller and Robbins (5), who demonstrated that all three types of poliomyelitis virus can be grown in non-neural tissue culture prepara-

tions. They also provided the tools for studying the safety and effectiveness of a vaccine by discovering the fact that tissue culture infected with poliomyelitis virus exhibits specific changes, the cytopathogenic effect, which can be specifically neutralized by an antiserum of the same serologic type.

The stage was now set for the development of a vaccine made by growing virus in tissue culture and killing it by some method which does not destroy antigenicity. This seemed to be a rather easy task, but even before the 1954 field trials of the Salk vaccine, an event occurred which should have served as a red flag. A group of workers at Camp Dietrich had prepared formalinized vaccine against Venezuelan equine encephalomyelitis and had tested it, not only by the usual safety procedures but by inoculating fairly large numbers of most animals susceptible to that disease. None of the animals became infected but, when the same vaccine was administered to people, at least 24 cases of encephalitis occurred (6). Earlier than this there had been adequate warnings from the 1935 experience with the Brodie and Kolmer poliomyelitis vaccines, which apparently caused about 20 cases of poliomyelitis among vaccinated individuals.

There seems to be no question that with poliomyelitis virus there is a much narrower margin between the points of destruction of infectivity and of antigenicity than is the case with some other viruses. Furthermore, it appears much more difficult to determine when the infectivity of the virus is destroyed. Thus, in our own earlier studies with formalinized preparations, we inoculated monkeys by the intramuscular route with vaccine which appeared to be non-infectious on the basis of what then seemed to be adequate safety tests, but poliomyelitis developed in some of the animals. We soon discovered, as others did, that it is necessary to use safety tests which were unthought of even two or three years ago, such as inoculation of a number of large bottles of tissue culture with 50 ml. of vaccine and inoculation of large numbers of monkeys. Recently the monkey test has been made more sensitive to live virus by making the monkeys more susceptible by the administration of cortisone. Although there is no question that the present tests are much more likely than the older tests to detect minute amounts of live virus, it is still not known whether they will detect every particle of live virus which may be present. It is probable that the average person inoculated with one or two particles of live virus will not contract poliomyelitis but the occasionally highly susceptible individual may.

Adoption of the newer safety tests and of new procedures in manufacture brought out the fact that some of the formalinized material being manufactured could not meet these new standards. So much difficulty was encountered in fact that, on recommendation of Salk and a special committee of experts, the U. S. Public Health Service in November 1955 promulgated a requirement that all manufacturers of the vaccine should filter it twice during the processing in order to remove debris or clumps of virus which were thought to be interfering with the inactivation process. This development undoubtedly increased the safety of the vaccine but it would appear that filtration subsequent to formalinization removes a good deal of inactivated virus which is precipitated by formalin and thus decreases antigenicity of the vaccine. Very recently, tests

made in my laboratory with prevaccination and postvaccination sera from young children receiving commercial vaccines produced by several manufacturers indicate that the product of at least one manufacturer does not possess good antigenicity. Additional testing of this sort should be carried out before any broad conclusions can be drawn. However, it is of the utmost importance that such investigations be made by as many laboratories as possible, because if fairly large numbers of vaccinated children should contract paralytic poliomyelitis, it may be concluded that all types of killed polio vaccines are ineffective, whereas it may be that only a certain method of production of the vaccine is unsatisfactory.

There are some who still believe that all killed-virus vaccines are ineffective and, therefore, that a completely inactivated poliomyelitis vaccine cannot be expected to be antigenic. Many years ago it was shown that by the use of killed-virus vaccine it was possible to immunize guinea pigs against equine encephalomyelitis so solidly that they resisted challenge with all the high-titer active virus that it was possible to put into their brains. Studies made with rabies and influenza virus vaccines have led to similar conclusions. In 1955 it was shown in an excellent study by Collier *et al.* (7) of the Lister Institute that high grade immunity could be produced in animals with an ultraviolet inactivated smallpox vaccine. It appears, therefore, that killed virus vaccines are effective if the method of killing is gentle enough not to destroy antigenicity.

Because of our earlier good experience with ultraviolet irradiated vaccines, (8), especially those for rabies and influenza, we have been working for several years with poliomyelitis vaccine prepared by this type of inactivation. In a paper which is in press (9) we have shown that, using ultraviolet-inactivated vaccine which conforms with all of the recent safety requirements, it is possible to stimulate good antibody production in a high percentage of young children living in a rural area which has been nearly free of poliomyelitis for a number of years. These children were so "immunologically inexperienced" that, prior to vaccination, 75 per cent had no detectable antibodies to Type I virus, 63 per cent had none to Type 2 virus, 61 per cent had none to Type 3 virus, and 42 per cent had none to all three types. These children held their antibody levels well for more than a year after vaccination, and there was a good response to a booster injection at that time.

The extent to which poliomyelitis antibody levels reflect immunity to paralytic disease is still unknown. In the 1954 field trials the 6-year-old children manifested as good antibody levels as the 7-year-olds and 8-year-olds, but their immunity to paralytic poliomyelitis was much lower (10). It will be of interest to see the degree of immunity in preschool children following the present vaccination campaigns. If there is relative failure, it may be necessary to develop and employ better prophylactic procedures in these age groups as was done so successfully for diphtheria and tetanus.

Other effects of the poliomyelitis vaccination program will be watched with interest. Will the vaccination of children increase the trend of paralytic poliomyelitis toward adults? Will it prevent poliomyelitis in whole areas by preventing

the virus from growing in the enteric tracts of vaccinees, thus blocking the chain of causation? Will it prevent only some of the cases which would otherwise have occurred? All these and other questions which are being asked will be answered, I hope, by the 1956 experience.

If the present killed-virus vaccinations should prove ineffective or fail to produce lasting immunity, it is possible that a live-virus vaccine will be developed and used either alone or in conjunction with a killed-virus vaccine. As early as 1950, Koprowski and his colleagues (11) fed children with an attenuated Type 2 virus; none contracted the disease, and most were found to have good antibody levels. Feeding experiments with virus attentuated by various methods have been carried out by others since then. Although the numbers of persons vaccinated in this way are still too small to permit us to draw definite conclusions, it appears that these vaccines may be safe for the vaccinees themselves. However, it is not yet certain that the virus may not regain virulence following serial passage from the vaccinee to other persons. Until questions such as this are solved, public health authorities will probably be loathe to have any studies made with live-virus vaccines outside of institutions.

COMMENT

Mention was made earlier in this paper of the effect of methodologic developments on progress in this field. The effect of the discoveries of Enders and his colleagues in the field of tissue culture is yielding rich results in directions other than poliomyelitis research. Enders and Peebles (12) have made important discoveries which may lead to general use of a measles vaccine. A tissue-culture rabies vaccine, free from the dangers inherent in brain-tissue vaccines, may be feasible. Huebner and his colleagues (13), by culturing tonsillar and adenoidal tissue, have brought to light a whole host of new viruses which cause respiratory disease and probably keratoconjunctivitis—the APC group. Promising results have already been obtained (14) with a vaccine against viruses of this group which cause the more serious types of disease, resembling influenza. Other studies are being made with the hope of producing vaccines which will be effective against such diseases as 1) German measles, the plan being to vaccinate all newly married women who have not had the disease recently, and 2) infectious and serum hepatitis, which seem to have increased so greatly in incidence and importance in recent years.

If vaccines should be made available for all of these diseases, one might wonder how it will be possible to vaccinate against them in addition to vaccinating against those diseases for which the procedure is now routine. It seems certain, however, that the same ingenuity which has made these vaccines available, will also provide for their incorporation into multiple antigens. A combination of poliomyelitis vaccine with diphtheria and tetanus toxoids and pertussis vaccine already appears to be feasible; combinations of other vaccines such as influenza and APC will undoubtedly be provided, if this is required. We have reached that fortunate stage at which apparently we no longer have to worry too much about the great plagues of the past; our principal preoccupation in the

future may be with the common cold and such nuisance diseases as herpes simplex. Possibly the hard won victories that have been cited may lead us to new triumphs over leukemia, or even over other types of cancer. On the other hand it must be kept in mind that there may be a new challenge—from unknown diseases that may rush in to fill the vacuum created if and when we shall have conquered our present enemies.

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TREATMENT AND PROGNOSIS IN ELDERLY PATIENTS WITH CANCER OF THE CERVIX*

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A previous study of many hundreds of patients treated at the Mayo Clinic for cancer of the uterine cervix has shown the average age of these patients to be 49 years (1). However, cancers of the cervix are found in the 20-to-35-year age group as well as in the 70's and 80's; the youngest patient on record at the clinic was a girl of 13 years (2).

Many physicians specializing in the treatment of cancer consider the prognosis to be very serious when confronted with cancer of the cervix in a young patient, or indeed when planning treatment for children or young adults afflicted with any type of cancer in any organ. It appears logical that the cancer will grow more rapidly in young tissues, whereas in the older patient there is a general slowing down of metabolism and cell growth, and therefore the rate of cancer growth should be similarly retarded. Perhaps the tragedy of encountering such a serious disease in a young person influences our thinking.

Several years ago a study of results in all patients treated with radiation for cervical cancer at the clinic from 1915 through 1944 showed that patients of 49 years or less did not obtain as good a result as those past 49 years of age (1). For instance, of 36 traced patients aged 20 to 29 years, only 25 per cent survived for five years, whereas of 218 patients in the 60-to-69-year age group 43.6 per cent had a five-year survival.

Methods of treatment have changed in recent years. To see if the older patient still had a better outlook than the young person, we recently studied results of treatment in young patients—those up to, but not including 36 years of age (3). One hundred and sixty-nine patients treated in the period 1940 to 1949 inclusive were 35 years of age or younger. Combined radium and roentgen therapy was the method of treatment in 66.3 per cent of the total; surgical treatment alone in 7.1 per cent; and combinations of surgical treatment and radiation in 16.6 per cent. Radium treatment alone or roentgen therapy alone was used in the remainder. One hundred and fifty-nine of the 169 patients, or 94 per cent, could be traced. The five-year survival rate in the traced patients was 53.5 per cent.

Our purpose in this paper is to compare the late results of treatment in patients aged 60 years or over with those in the previously reported group of young patients.

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CLINICAL DATA

During the same ten-year period, 1940 to 1949 inclusive, 217 patients aged 60 years and over were treated. Two hundred and five, or 94 per cent, could be traced. Table 1 shows the age distribution, with the majority of the patients in the 60-through-65-year group and diminishing thereafter to 2 in the 81-through-85-year group. Most of the lesions in these cases were squamous-cell epitheliomas; the heading "other malignant lesions" includes adenocarcinomas, adenoacanthomas, and hemangio-endotheliomas. The "modified" group means patients who had received treatment elsewhere, but who still exhibited invasive cancer. Table 2 depicts the symptomatology, which was not appreciably different from that of the young group. Vaginal bleeding was the complaint of the largest number, followed by leukorrhea; pain as a symptom usually denoted a far advanced lesion.

Results of therapy are shown in Tables 3–5. Nine patients were traced (Table 3); in these, the surgical approach was employed. Five of the 9 survived for five years or longer.

The outcome in the larger group treated by irradiation is depicted in Table 4. This includes 209 patients, only 1 of whom had surgical treatment. One hundred and ninety-two of the 209 could be traced. Of the 132 traced patients having complete irradiation therapy, 56.8 per cent (an encouraging figure) appeared

TABLE 1

Carcinoma of the Cervix in Elderly Women: Age Distribution

	60 Through 65 Years	66 Through 70 Years	71 Through 75 Years	76 Through 80 Years	81 Through 85 Years
Squamous-cell epithelioma					
Stage I	13	4			
Stage II	37	13	2	2	
Stage III	34	13	12	2	1
Stage IV	25	8	2	1	
Other malignant lesions	16	6	3	1	1
Modified	19	2			
Total	144	46	19	6	2

TABLE 2

Carcinoma of the Cervix in Elderly Women: Symptoms

Symptoms	Cases
Vaginal bleeding	169
Leukorrhea	25
Pain	12
Symptoms in urinary tract	4
No symptoms	7
Total	217

TABLE 3

Carcinoma of the Cervix in Elderly Women: Survival After Surgical Treatment

	Lived 5 or More Years After Operation	Dead
Wertheim hysterectomy—Stage I	1	
Wertheim hysterectomy—Stage I		1
Total abdominal hysterectomy and bilateral salpingectomy—Stage I		1
Total abdominal hysterectomy and bilateral salpingo-oophorectomy—Stage I Anterior resection of sigmoid for adenocarcinoma of rectum Unsuspected squamous-cell epithelioma of cervix	1	
Total abdominal hysterectomy and bilateral salpingectomy—Stage I	1	
Wertheim—Stage I (recurrent in vagina 12 years after operation) (no nodes dissected)	1	
Wertheim hysterectomy—Stage III Positive obturator nodes on left	1	
Wertheim hysterectomy—Stage IV		1
Subtotal hysterectomy and bilateral salpingo-oophorectomy—Stage IV		1
Total	5	4

TABLE 4

Carcinoma of the Cervix in Elderly Women: Survival After Radiation Therapy by Type of Therapy

Type of Radiation Therapy	Total Patients	Traced Patients	Lived 5 Years or More After Treatment	
			Number	Per cent
Complete radium and roentgen therapy	142	132	75	56.8
Complete radium	8	7	4	
Palliative therapy, limited radium and roentgen	27	25	7	28.0
Limited radium	16	12	0	
Abandoned radium	5	5	0	
Roentgen	10	10	1	
Postoperative roentgen	1	1	1	
Total	209	192	88	45.8

well five or more years after treatment. The five-year survivals of the entire radiation group dropped to 45.8 per cent, since only 28.0 per cent of the patients treated with a limited course of radiation for palliative purposes survived for five years.

In Table 5 the data for the entire group of 217 patients treated either surgically or by radiation are summarized. Two hundred and five patients could be traced. Of these, 45.4 per cent survived for five years. Good results in stages I

TABLE 5

Carcinoma of the Cervix in Elderly Women: Survival After All Forms of Treatment by Type of Lesion

Type of Lesion	Total Patients	Traced Patients	Lived 5 or More Years After Treatment	
			Number	Per cent
Squamous-cell epithelioma				
Stage I	17	16	11	68.8
Stage II	54	49	31	63.3
Stage III	62	61	27	44.3
Stage IV	36	35	14	40.0
Modified	21	17	5	29.4
Other malignant lesions	27	27	5	18.5
Total	217	205	93	45.4

and II were offset by poor results in the "modified" group and in the number with malignant lesions other than squamous-cell epithelioma. It is obvious from the survival percentages in stages III and IV that during the period of analysis there has been a tendency to overstage the malignancy in this age group. Factors tending to influence staging are the rigidity and atrophy of the vagina, and the normal loss of pelvic mobility in this age group. Moreover, the presence of other pelvic tumors, or of residua of inflammation or surgical treatment, is more common with advancing age.

SUMMARY

Results of treatment of cancer of the cervix in patients aged 60 years and more, treated in the period 1940 through 1949, have been reviewed and a comparison made with previously published results of treatment of this disease in younger patients—those up to, but not including, 36 years of age.

In the younger group, surgical treatment alone was used in 7.1 per cent of the patients, and surgical treatment with irradiation in 16.6 per cent. Obviously the younger patient is a better surgical risk. In the older patients, only 4 per cent underwent operation. The five-year survival rate turned out to be more encouraging in the younger group, the study of both groups covering the same years. Of 159 traced patients in the younger group, 53.5 per cent survived for five years, in comparison with 45.4 per cent of 205 traced older patients.

This result may alter the unfavorable opinion regarding prognosis held by some of us when confronted by cancer of the cervix in young patients.

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POLYACRYLIC RESIN: EFFECTIVE HYDROPHILIC COLLOID FOR THE TREATMENT OF CONSTIPATION*

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The use of hydrophilic colloids for the treatment of constipation is well recognized. Tainter and Buchanan (1) have classified eight types of colloidal laxatives, of which four are extensively used today. These include agar-agar, tragacanth gums, psyllium gums and the synthetic derivatives of methyl cellulose. We wish to add to this list by reporting on a new series of synthetic resins[1] which possess exceptionally high water-binding capacity. *In vitro* studies with synthetic gastric and intestinal juices indicate that the water-binding capacity of these resins is three to ten times that of other hydrophilic colloids. After many trials, the hydrophilic polyacrylic type of resin was chosen for this investigation. It has a capacity to bind 70–105 milliliters of water per gram when dispersed in distilled water and 70–94 milliliters per gram when dispersed in synthetic intestinal juice. This particular resin is characterized by hydrogen occupying the cation exchange position. The ionic exchange capacity for sodium is negligible—only 1 to 3 per cent. Like resins of comparably high molecular weight, it is not absorbable from the gastro-intestinal tract and, except for its hydrophilic effect and low cation exchange capacity (*in vivo*) it is physiologically inactive during transit through the gastro-intestinal tract. Our experiences with other synthetic resins of different ionic cycles (a hydrophilic polysulfonic resin and hydrophilic polycarboxamide resin) were not satisfactory for the treatment of the patients discussed in this report.

METHODS

Various techniques have been recommended for the measurement of laxation. These vary from double-blind observations to actual measurement of the total daily bulk, fluidity or physical state of the fecal mass. In a previous review by one of us (2), it was noted that disturbances in the act of defecation are the most important reason for chronic constipation. The development of dyschesia with loss of the defecation reflex may lead to fecal impaction in susceptible patients. Since institutionalized patients, particularly those bedridden because of neurologic disorders, present this problem as a serious aspect of chronic care, any means which will overcome fecal inspissation and development of fecal impaction is of definite value. These patients represent the severest test for the evaluation of laxative agents. In contrast to the majority of persons with

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[1] White Laboratories, Inc. Kenilworth, N. J. supplied various polycarboxylic resins and other aid for this investigation.

constipation, in whom subjective phenomena play a predominant role, this group of institutionalized patients presents an objective measure for evaluating the effectiveness of laxative agents. If unsuccessful, fecal impaction is the rule, with associated recurrent bouts of intestinal obstruction and alternating periods of diarrhea and constipation. Extensive nursing care with repeated enemas and manual removal of the fecal contents are required in the absence of effective laxation. Such were the hospitalized subjects used for this study. If the resin maintained its high water-binding capacity in intestinal and fecal juice, then fecal impaction would be less likely to occur and nursing care would be minimal.

Utilizing this rigid criterion for effectiveness, we followed in 37 hospitalized bedridden patients the results of continuous oral administration of 1.5 to 4 grams daily of the polyacrylic resin for periods ranging from three weeks to several months. The preparation was given in the form of capsules, which facilitated daily administration.

RESULTS

Bedridden patients

A demonstrable improvement in bowel function was noted, in 23 of the 37 patients treated—66 per cent (Table 1). However, the dosage of 3 grams daily or less was satisfactory in only half of the 10 patients so treated. When 4 grams of resin was used in 31 trials (including 4 patients previously studied with the smaller dosage) it was effective in 71 per cent. Seven of the patients not responding to therapy failed to do so because of inadequate irregular dosage or because the concomitant administration of potent analgesics prevented any control of bowel function. When this was taken into account, the resin was effective in 82 per cent of the trials.

Improvement was noted in the majority of patients within three to seven days; in others a period of two to three weeks of continuous administration was required before any change was noted in the severity or degree of fecal impaction. The first objective sign was increased ease of removal of fecal material by enema or by manipulation. With continued use of the resin, the patient might have a spontaneous bowel movement but impaction would still occur at infrequent intervals. Subsequently, the intervals between fecal impaction would become longer, and the patient would have soft bowel movements spontaneously.

TABLE 1

Effectiveness of Polyacrylic Resin in Bed-Ridden Patients

Daily Dose	No. of Patients	Control of Constipation			Per Cent Showing Improvement
		Complete	Partial	None	
3 Gm. or less	10	2	3	5	50
4 Gm.	31*	18	4	9	71

* In 4 subjects both dosages were used.

Typical case records were as follows:

M. M., aged 47, had multiple sclerosis. This patient required repeated laxatives and enemas every few days for episodes of fecal impaction. Therapy with resin was begun using a dosage of 1 Gm. three times daily. When no effect was noted, the dose was increased to 4 Gm. daily. Within a few weeks, there was complete control of bowel function without need of enemas or laxatives. Any discontinuation of the medication immediately resulted in fecal impaction. When bowel function was controlled, it was possible to decrease the resin to 1 Gm. twice daily with continuation of effect.

A. C., aged 70, had hemiplegia and Paget's disease. This patient had repeated bouts of fecal impaction with continuous use of laxatives, mineral oil and enemas. With 1 Gm. of resin daily, no effect was noted. When the dose was increased to 1.5 Gm. daily and subsequently to 3 Gm. daily for the total period of forty-six weeks, there was complete control, with normal spontaneous bowel movements and no need of laxatives or enemas.

Ambulatory patients

With assurance that the polyacrylic resin could decrease the need for laxatives and enemas and restore normal bowel function, the study was expanded with reference to ambulatory patients who had the subjective complaint of chronic constipation. In all but 3, who had noted disturbed bowel function for only about a year, the constipation had existed for several years or for "entire" life of the patient. All but 1 required laxatives or enemas repeatedly. In the majority, these measures were required for any bowel movement. Various dosage schemes of the resin were tried. This material was available at first as 450-mg. capsules and subsequently as 500-mg. capsules. One or two capsules were administered three to four times daily as the priming dose. Therapy was continued from one to forty-eight weeks; 11 patients were observed for over twelve weeks. Satisfactory control of bowel function resulted in 23 of the 37 ambulatory patients. A dosage of 450 mg. three or four times daily was not satisfactory, since only 4 of the 11 trials were effective. It was possible in 4 of these 7 unresponsive patients to observe the effects of an increased dose. Control of bowel function was attained thereby in 3 of the 4. However, in view of the inadequacy of this small initial dosage, the effectiveness of the resin in ambulatory patients should be judged only on the basis of results with the optimum or higher dosages. Thus, 31 patients were followed with the higher dosage; of these, 24 or 77 per cent, established effective control of bowel function (Table 2). As in the case of the bedridden patients, improvement was noted within a few days to two weeks of continuous therapy.

Once daily a bowel movement without laxatives or enemas was attained, it was possible in 15 patients to observe the likelihood of continued control of bowel function with decreasing doses of resin. Thirteen of these 15 patients responded to the smaller maintenance doses, and in 7 patients it was possible subsequently to discontinue the resin and yet have normal bowel function without laxatives.

Signs of intolerance were negligible. None of the bedridden patients had any untoward gastro-intestinal manifestations. Four of the ambulatory patients, had abdominal distention, flatulence or "gas"; but in 2 of these, the gastro-intestinal

TABLE 2

Effectiveness of Polyacrylic Resin in Ambulatory Patients

Daily Dose	No. of Patients	Control of Constipation			Per Cent Showing Improvement
		Complete	Partial	None	
450 mg., three or four times daily	11	4	—	7	36.3
900–1000 mg., three or four times daily	31	22	2	7	77.4

symptoms disappeared with continuation of the medication. In 2 additional patients, the priming dose may have been excessive and the relatively sudden increase in bowel movements could be described as diarrheal in type; with adjustments of dosage, this condition subsided. There were no idiosyncrasies or disturbances in nutrition. Although the sodium exchange capability of the resin was no higher than 3 per cent, we observed the patients carefully for edema formation; regardless of dosage or duration of resin administration, no edema was noted. The resin apparently did not interfere with absorption of other drugs required for specific treatment of medical problems. None of the patients complained of anorexia or fullness of the stomach—symptoms which would suggest bulk formation and interference with gastric contents. The resin did not alter any of the constituents of urine or blood. Various other tests made occasionally with reference to the underlying medical problem failed to reveal any abnormality attributable to the resin medication.

DISCUSSION

The treatment of chronic constipation and correction of the cathartic habit have been the subject of numerous reviews (3). It is readily recognized that constipation is not only a state of mind in most patients who use laxatives excessively, but also that over a period of years the abnormal condition of bowel function has more or less been set in patterns acceptable to the patient. The continued use of cathartic agents, regardless of potency or mechanism of action, probably also conditions the rectum or other parts of the gastro-intestinal tract to be responsive only when the abnormal stimulation of "cathartic effect" is repeated. Patients who fit into this category, therefore, are usually not responsive to controlled studies, because the conditions that have been built up over many years may not be duplicated by use of the investigative medications.

Attempts at breaking the cathartic habit by administration of bulk-producing agents such as bran, agar, tragacanth, psyllium seed, and methylcellulose derivatives have all been reported, but have not aroused the enthusiasm of the medical profession. Although theoretically "bulk-producing hydrophilic colloids" are desirable, since they may promote defecation without concomitant irritation of the bowel, their acceptance has been limited. Some hydrophilic properties of these agents become decreased to a negligible degree in intestinal and fecal juice, and their effectiveness is regulated almost entirely by the total amount of medication ingested.

The hydrophilic colloidal properties of the polyacrylic type of polycarboxylic resins have overcome the deficiencies of the other preparations. The water-binding capacity per gram of material is maintained throughout the gastro-intestinal tract from stomach to rectum. An initial dosage of 4 grams daily will result in a jell-like fecal mass of approximately 300 grams. Since this is devoid of all irritation, except that produced by bulk, it is well tolerated. Effectiveness is achieved with surprisingly small amounts of medication, which is in contrast to other hydrophilic preparations. Patient acceptance is a varying experience. At onset of use, since the hydrophilic properties do not become apparent for several days, the patients' desire to continue is low. However, a little later, when the bowel starts to function daily with unanticipated changes in the consistency and size of the stools, acceptance is no problem. It is recognized that the daily use of this type of laxative is merely a substitution rather than a correction of bowel dysfunction. It was therefore gratifying to find that with gradual reduction in the dosage of resin and sometimes complete discontinu-

TABLE 3

Classification of Factors Accounting for Constipation in Bedridden Institutionalized Patients

I. *Institutionalization itself*
  A. Psychologic
  B. Environmental
    1. Unsatisfactory facilities
    2. Delay of toilet facilities
  C. Constipating medications
  D. Dietary restrictions and alterations
  E. Bed rest—postural requirements
II. *Disturbances in gastro-intestinal motility*
  A. Inadequate stimulation
    1. Chemical
      a. Intestinal contents
      b. Medications
      c. Hormones
    2. Mechanical
      a. Dietary
  B. Decreased excitability of gastro-intestinal mucosa
    1. Disease states
    2. Medications
  C. Diseases of nervous system
III. *Disturbances in act of defecation*
  A. Previous improper training and neglect
  B. Previous abuse of laxatives
  C. Diseases of the colon or rectal mucosa
  D. Diseases of the anal sphincter
  E. Diseases of the nervous system
  F. Medications
IV. *Disturbances in expulsive power*
  A. Atony of intestinal musculature
  B. Weakness of pelvic floor
  C. Inefficiency of diaphragmatic movements
  D. Weakness of abdominal-wall muscles

ation, some patients could maintain normal bowel function, even if they had been accustomed to using other laxative agents for many months or years.

Of greater importance were the excellent results obtained in our hospitalized bedridden patients. In Table 3 is a classification of the various factors accounting for constipation in institutionalized patients. When the problem of fecal impaction was considered, diseases of the nervous system (all types) and disturbances in the act of defecation were the major etiologic factors in the patients included in this study. The overcoming of dyschesia within a few weeks of therapy and thereafter in many patients, and the restoration of spontaneous bowel movements without aid of enemas or irritating cathartics, were results heretofore not seen in our institution. All other measures previously used, including the available hydrophilic colloids, had proved to be unsatisfactory.

SUMMARY AND CONCLUSION

1. A new synthetic polyacrylic resin of the polycarboxylic type with high water-binding capacity in intestinal and fecal juice is an effective hydrophilic colloid for the treatment of chronic constipation.

2. In hospitalized bedridden patients having frequent bouts of dyschesia and fecal impaction, the resin restored bowel function in 71 per cent of the trials.

3. In ambulatory patients, correction of subjective complaints of constipation was achieved in 77 per cent of the trials.

4. In some ambulatory patients, with disappearance of constipation, it was possible to decrease or to discontinue the use of resin and still maintain normal bowel function.

5. Daily administration of the resin for periods ranging up to two years of continuous use proved to be safe and there was no evidence of gastro-intestinal irritation or systemic toxicity.

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HYPOTHERMIA AS AN ADJUNCT IN THE SURGICAL TREATMENT OF CARDIOVASCULAR DISEASES*

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Cooling of part of the body as an analgesic procedure has been known for many years. The early savages and our own American Indians learned that immersing an injured part in cold water not only relieved pain but seemed to reduce the chances of inflammation. In modern times, the ice collar, ice bag, and cold pack all have the same therapeutic implications.

The clinical use of ice as an anesthetic agent dates back to the work of Fay and Smith (1) who, in the late 1930's, began to treat hopeless malignant conditions. It was found that with the use of ice the amount of sedation necessary for the patient's comfort could be lessened and inflammatory processes due to secondary infection were markedly reduced. In surgery, refrigeration was used as an anesthetic for amputation. Allen and associates (2, 3) were early users of this method and in 1942 one of us (4) could report on 100 major amputations performed with the application of ice as the only anesthetic. Such treatment was necessary because of the high mortality rate under general anesthesia when uncontrolled diabetics and hopeless arteriosclerotics presented septic limbs which had to be surgically removed. Since that time, Lange *et al.* (5), Lewis (6), Talbott (7), Cookson *et al.* (8), Bigelow *et al.* (9), McQuiston (10), and others have contributed greatly to the utilization of refrigeration in the field of surgery.

SOME EFFECTS OF HYPOTHERMIA

Heart action and oxygen consumption. Oxygen consumption declines progressively and proportionately with the degree of hypothermia, provided oxygen saturation is maintained and shivering is prevented. At 20°C. there is only 15 per cent of the normal oxygen saturation. There is also a definite decrease in the mechanical output of the heart.

Heart failure after aortic occlusion. When the thoracic aorta is clamped, there is rapid dilatation and failure of the left ventricle and ischemia distally. If the animal is cooled to 26°–30°C., heart failure can be delayed and the effects of distal ischemia are also delayed.

Ventricular fibrillation and potassium balance. Ventricular fibrillation is the great danger in refrigeration (Table 1). A sudden rise in the level of blood CO_2 and a shift in the serum potassium concentration appears to cause fibrillation in

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dogs. If the pH can be kept high, the incidence of fibrillation is definitely lower and thus hyperventilation of the patient reduces the chances of fibrillation. The serum potassium level drops as the temperature falls. (Potassium chloride injected into the cold dog's coronaries defibrillates many such hearts.) Excitability of the myocardium and, in particular, of the cardiac cells, is increased by hypothermia. Thus, the real danger—fibrillation—can be reduced by the adequate ventilation and, if necessary, infusion of the coronary system with potassium chloride.

Effect on the myocardium, brain and spinal cord. With hypothermia, the myocardial cells become more sensitive to ischemia and anoxia, but the brain cells become less sensitive to ischemia. The brain cells begin to die when they are deprived of oxygen for three minutes and the changes are irreversible after four to five minutes. The time can be lengthened to thirty minutes by hypothermia at 26°C. Normally, the circulation of the spinal cord can be shut off for only ten minutes without damage. With hypothermia, the cord can withstand ischemia up to ninety minutes.

Clinical neurologic changes. The effects of hypothermia, as observed on patients at St. Vincent's Hospital, are shown in Table 2. It is apparent that with increasing hypothermia there is loss of neurologic reactions.

Shivering. Shivering is a reflex phenomenon due to exposure to cold. It has an adverse effect, however, in the clinical use of hypothermia. It causes fatigue and increases oxygen consumption. Shivering, therefore, must be controlled. In-

TABLE 1

Effects of Hypothermia

I. *Ventricular Fibrillation* (below 28°C.)

Accumulation of carbon dioxide in blood (prevented by hyperventilation).
A fall in serum potassium level increases myocardial irritability.

II. *Neurologic Changes after O_2 Deprivation* (26°C.)

Time before death of brain cells increased from 3 to 30 minutes.
Time before death of cord cells increased from 10 to 90 minutes.

TABLE 2

Observations on Hypothermia Patients

(St. Vincent's Hospital)

Temperature	37–35°C. (98–95°F.)	35–32°C. (95–90°F.)	32–29°C. (90–85°F.)	29–26°C. (85–80°F.)
Level of Consciousness	Complete	Calm	Stuporous	Unconscious
Reflex excitability				
Shivering	++++	Ceases	0	0
Swallowing	++++	++	+	0
Eyelid blink	++++	++	0	0
Pharyngeal	++++	+++	+	0
Skin stimulation	++++	+++	+	0
Laryngeal	++++	+++	++	+

duction of general anesthesia prior to hypothermia seems to be the safest and most certain way of preventing shivering.

Renal effects. Refrigeration anesthesia appears to interfere with normal kidney function only to the degree that other anesthetic agents interfere with it.

Pulse rate, blood pressure and respiration. The systolic and diastolic blood pressures and the cardiac and respiratory rates fall in a definite manner during hypothermia. Our findings are shown in Table 3.

Electrocardiogram and muscular tone. The effects of refrigeration on the electrocardiogram and muscular tone are shown in Table 4. Muscle tone decreases and the muscles become relaxed.

Hemorrhage. The experimental dog dies three minutes following major hemorrhage, unless infused. With hypothermia, this time-period can be prolonged to twenty-five minutes. It has been shown by Slattery *et al.* (11) that if dogs are bled so that the blood pressure decreases to 40 mm. of Hg, and are then transfused, only 20 per cent live twenty-four hours and 13 per cent are alive at one month (Table 5). If a similar experiment is performed under hypothermic conditions, 93 per cent of the dogs are alive at twenty-four hours and 80 per cent are alive at one month (11). Thus, with hypothermia, the subject can survive a greater degree of hemorrhagic shock.

CLINICAL USE OF HYPOTHERMIA

From these observations one arrives at two facts. *A.* The use of refrigeration permits lengthening of the period during which the major blood supply can be cut off without irreversible damage to the brain, cord and heart. *B.* There are dangers inherent in the use of this method, the greatest of which are ventricular fibrillation, cardiac arrest and sometimes death. To justify its use, therefore,

TABLE 3

Effect of Hypothermia on Blood Pressure and Cardiac and Respiratory Rate

	Initial Fall	Fall for Every 3°C.
Systolic B.P.	20%	10%
Diastolic B.P.	15%	10%
Cardiac Rate	25%	12%
Respiratory Rate	30%	15%

TABLE 4

Observations Hypothermia Patients

(St. Vincent's Hospital)

Temperature	37–35°C. (98–95°F.)	35–32°C. (95–90°F.)	32–29°C. (90–85°F.)	29–26°C. (85–80°F.)
ECG changes	None	Slowing	Bradycardia	Prolonged QT interval
Muscular tone	No change	Slight decrease	Marked decrease	Excellent relaxation

TABLE 5

Effect of Hypothermia in Massive Hemorrhage in Dogs (Slattery (11))

Without transfusion	
Normothermia	Dog dies in 3 minutes
Hypothermia	Dog dies in 25 minutes

With transfusion		
	24-Hour survival	One-month survival
Normothermia	20%	13%
Hypothermia	93%	80%

the indication must be one in which the lack of correction is a greater hazard than the danger inherent in refrigeration. Certain operations on the heart and the brain, or operations in which great blood loss is to be expected, can be accomplished only when the circulation is shut off; this requires either an extracorporeal pump or the method described.

We are all expecting announcement of the ideal oxygenator pump for extracorporeal circulation to permit operations under conditions in which the heart and lung mechanism is entirely stopped and a dry field is created. For forty years, however, attempts have been made to produce such a pump. Such an oxygenator seems near completion and has served satisfactorily in many clinics. Nevertheless, the mortality rate, even under ideal circumstances, in open operations on the heart is still high and a prohibitive figure to many.

Some patients with these defects cannot wait for the safe pump. In the meantime, with the use of hypothermia one can stop the heart for a reasonable time. For example, the heart can be opened and operated on for a period up to twelve minutes in both the monkey and man without permanent cardiac or brain damage. With hypothermia, occlusion of the blood supply to the brain and cord is possible for even longer periods of time before irreversible changes set in. Hypothermia permits certain operations otherwise impossible at present. It may be of use also in hyperpyrexia, extensive trauma, burns, and operations on debilitated patients. The indications for its use are listed in Table 6.

DISADVANTAGES OF HYPOTHERMIA

Disadvantages in the use of refrigeration techniques are summarized as follows:

Stress reaction to cold

The stress or shock reaction, which is an initial phenomenon, is a definite disadvantage. It can be minimized by the use of central autonomic blocking agents (chlorpromazine) and general anesthetic agents.

TABLE 6

Indications for the Use of Hypothermia

I.	*Intracardiac Procedures*
	A. Open technique (septal defects)
	B. Occlusion of great vessels
II.	*Congenital Cardiac Conditions*
	A. Lesions associated with cyanosis
	B. Transplantation of great vessels
III.	*Surgery Associated with Hemorrhage*
	A. Repair of aortic aneurysm
	B. Intracranial vessel surgery
	C. Vessel grafts to vital organs (selected)
IV.	*Toxic Conditions*
	A. Hyperpyrexia
	B. Severe liver dysfunction
V.	*Severe Stress*
	A. Extensive trauma
	B. Burns
	C. Major surgery in debilitated patients (especially children and infants)

Increased myocardial irritability

Increased cardiac irritability is a definite deterrent to the use of hypothermia and is related to temperature levels below 80°F. It can be overcome by careful attention to acid-base and electrolyte balance and to adequate ventilation. Cardiac cells subjected to hypothermia die in fifteen minutes if the circulation is shut off, in contrast to thirty minutes for brain cells.

Increased viscosity of blood and hemoconcentration

These blood changes are conducive to intravascular clotting. They can be controlled in part by the continuous infusion of crystalloidal solutions (5 per cent dextrose in water; sixth-molar sodium lactate). Administration of potassium lactate solution (Darrow) helps to protect the patient against ventricular fibrillation.

METHODS FOR INDUCING HYPOTHERMIA

There are three main methods for inducing hypothermia (Table 7).

Surface cooling method

Refrigeration blanket. Refrigeration can be induced by the use of a hypothermic refrigeration unit (Fig. 1). This mattress apparatus contains tubes through which a circulating refrigerant (30 per cent alcohol in water) is pumped. An electric pump and a solution of ice water and salt may be substituted. The temperature drops continually and slowly to 74°–80°F.

Morphine and scopolamine are used as premedication. General anesthesia is used to prevent shivering. A temperature of 84° to 88°F. is adequate for most operations although some have been performed at 80° and 81°F.

TABLE 7

Techniques for Inducing Hypothermia

I. *Surface Cooling*
  A. Refrigeration blanket
  B. Immersion
  C. Application of cold to great vessels; or refrigerant solutions in thoracic or abdominal cavity
  D. Regional refrigeration
    1) Extremities
    2) Heart and other organs

II. *Extracorporeal Circulation*
  Involves use of heart-lung apparatus

III. *Artificial Hibernation (pharmacologic)*
  A. Neuroplegia-autonomic blockade: (chlorpromazine)
  B. Administration of combined antihistamine, analgesic (Demerol) and neuroplegic drug (chlorpromazine, Laborit)

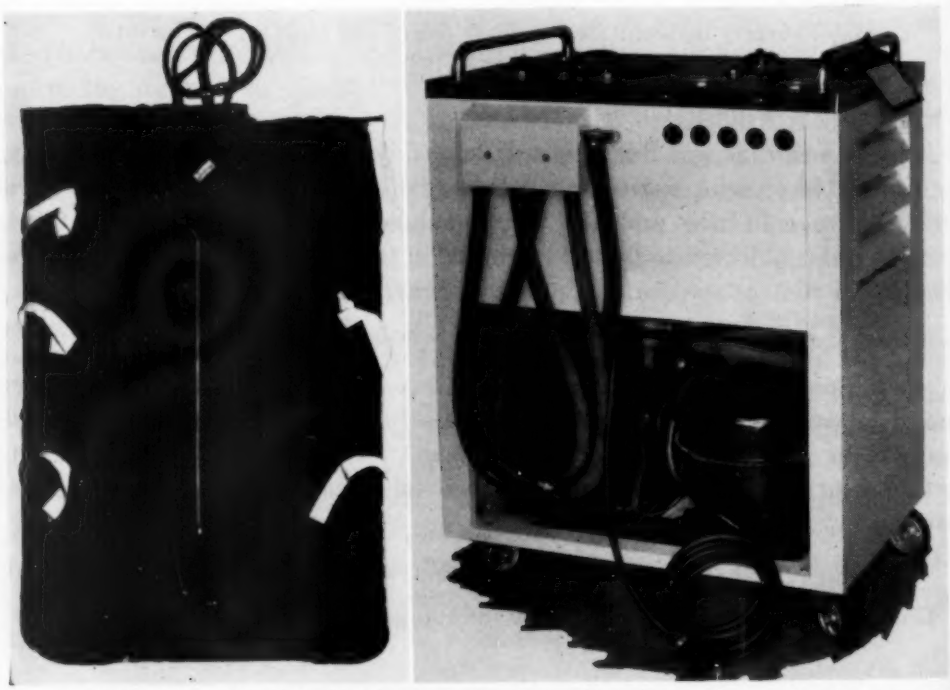

FIG. 1. **A.** Refrigeration blanket for inducing hypothermia. **B.** Apparatus for pumping refrigerant (Therm-O-Rite Products, Buffalo, N. Y.). The apparatus can also be used for rewarming.

The rate of cooling varies with the size of the patient. Two to four hours are required in adults but the temperature can be reduced to 74°F. in a child in one hour. In our experience the patient's temperature can be maintained at 88° to 92°F. with safety for three to five hours in long vascular operations.

At the termination of definitive surgery, rewarming of the patient begins. The

cold solution is changed to a warming one, and warming continued during the closure of the thorax or abdomen. It takes several hours to restore normal temperature with this method.

Immersion technique. For induction, an intravenous drip followed by cyclopropane and then endotracheal ether is used. The patient is immersed in a tub of ice water at a temperature of approximately 3°C. in the third stage of anesthesia, when the defensive reflex mechanism is obliterated. The patient's body temperature is observed carefully by means of a deep rectal or esophageal thermometer or thermocouple.

The rate of cooling is determined by the size of the patient and his adipose covering. It takes between twelve and thirty minutes to reach the desired temperature level, which is 28° to 23°C., depending upon the operation to be performed. The degree of cooling is followed proportionately by the risk of cardiac arrhythmia.

The length of the cooling time depends upon the operative procedure contemplated. The temperature should be reduced to 28°C. (82°F.) for an operation for pulmonary stenosis which takes four to five minutes. When an operation takes eight to ten minutes, as for an atrial septal defect, a temperature of 27° to 28.5°C. (80° to 83°F.) is necessary. Modified temperature of from 27° to 30°C. (80° to 86°F.) may be employed. When the operation is a life-or-death matter, a temperature of 21° to 22°C. (69° to 71.5°F) has been used but is not advised. The incidence of arrythmia and cardiac arrest increases in such instances and this added risk must be assumed. The temperature will drop from 1° to 6° after removing the patient from the immersion tank.

For rewarming the patient, the wounds are sealed with dermatone glue and the drains surrounded with pieces of rubber secured with the material used in Swann's technic. The patient is re-immersed in the tub at 45°C., and is removed again when the temperature reaches 32° to 34°C.

It is uncertain at this time whether gradual warming after certain operations would not be advantageous. The hibernating animal emerges gradually and resumes his normal function best under these circumstances. Experiments to determine whether slow warming, at least in some instances, would have therapeutic value are under way.

Combination of cooling apparatus and immersion. After rapid induction by immersion, cooling can be continued with a refrigerator blanket, thus permitting longer operations.

Direct application of cold to great vessels. Hypothermia can be rapidly induced by applying cold solutions directly to the major blood vessels. Ice bags along the great vessels have been used by some surgeons. In association with administration of ganglioplegic substances, the temperature can be lowered rapidly. Repeated flooding of the chest or abdominal cavity with cold saline can induce cooling.

Regional refrigeration. In the original refrigeration anesthesia technics for amputation, the limb was encased in ice for several hours before the operation.

With the use of the refrigeration blanket, amputation can be performed without further anesthesia except for local infiltration of the sciatic nerve. We have successfully performed over 100 amputations with this technic. Such regional cooling can be applied to other organs, including the heart.

Extracorporeal circulation

This method of inducing hypothermia requires the use of a heart-lung apparatus. The blood is removed, cooled and replaced. The technic is complicated.

Artificial hibernation (pharmacologic)

This technic of blocking heat production by central autonomic blocking agents requires concomitant analgesia or anesthesia. The neuroplegic autonomic blockage is accomplished by: 1) chlorpromazine, and 2) "lytic cocktails" consisting of an antihistamine, an analgesic and a neuroplegic substance (Demerol and chlorpromazine). Chlorpromazine appears to be the active principle in this method.

SUMMARY

Hypothermia may be used for anesthesia and is a valuable surgical adjunct in certain conditions.

It extends the time the circulation can be shut off and reduces the danger of ischemia of the brain, cord and peripheral tissues.

It permits open heart operations, with limitations, and is a good method for some types of this surgery, until a mechanical heart is perfected.

It should have greater application in operations in which massive hemorrhage is expected.

The serious danger of ventricular fibrillation must be accepted, and means of vigorous treatment should be available.

The critical temperature seems to be 28° to 28.5° C. Below this point, the danger of fibrillation increases.

It is likely that refrigeration apparatus will be an incorporated part of every operating table in the future.

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THE VALUE OF RADIOACTIVE ISOTOPES IN PHARMACOLOGICAL RESEARCH*

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ACKNOWLEDGMENT

Mr. President, Members of the American Therapeutic Society, and Guests:

Today, I come before you with a sense of deep appreciation of the singular honor which you have conferred upon me by selecting me as the recipient of the Oscar B. Hunter award for 1956. With your permission may I interpret your gracious recognition as your approval of the researches of a large number of graduate students and staff in the Departments of Pharmacology, Botany and Medicine in the University of Chicago. It is particularly gratifying that you, Mr. President, and your Society place such a very high value on basic research and that you appreciate the necessity of having an adequate stock-pile of information which is an essential prerequisite for advancing the frontiers of knowledge.

In the case of the atomic age, we have an excellent illustration of the great value of the basic researches which were carried out years ago and which enabled the architects to devise the crucial experiments which led up to the splitting of the atom.

INTRODUCTION

The impact of the atomic age on present-day society

Seldom, if ever, in the history of mankind has it been possible to fix not only the day of the year but the actual time of the day and year which marks the beginning of a new age having momentous importance to the human race. In the case of the Atomic Age, it is possible to say that it began about 3:25 p.m. on December 2, 1942, in a temporary war laboratory, under the West stands of Stagg Field at the University of Chicago. It was on that day and time that Enrico Fermi, one of the principal architects of the atomic era, pronounced the nuclear reaction self-sustaining (Fig. 1). This epoch-making experiment was carefully planned for many months and the success of it demonstrated the possibility of splitting the atom with the controlled release of tremendous and frightening energy. In plain language this dramatic and basic experiment proved for the first time that the splitting of the atom with the controlled release of large amounts of energy was feasible (1).

In 1948 Dr. Hugh Scott Taylor, in an address at the opening of the new Albertus Magnus Hall of Science at St. Thomas College in St. Paul, Minnesota, made the striking statement that with the reality of the chain-reaction process a potential source of power at least 40,000,000 times greater than was available prior to this discovery was put into the hands of man. Expressed in another way, "If you take the amount of energy available to man in 1942, and that includes all

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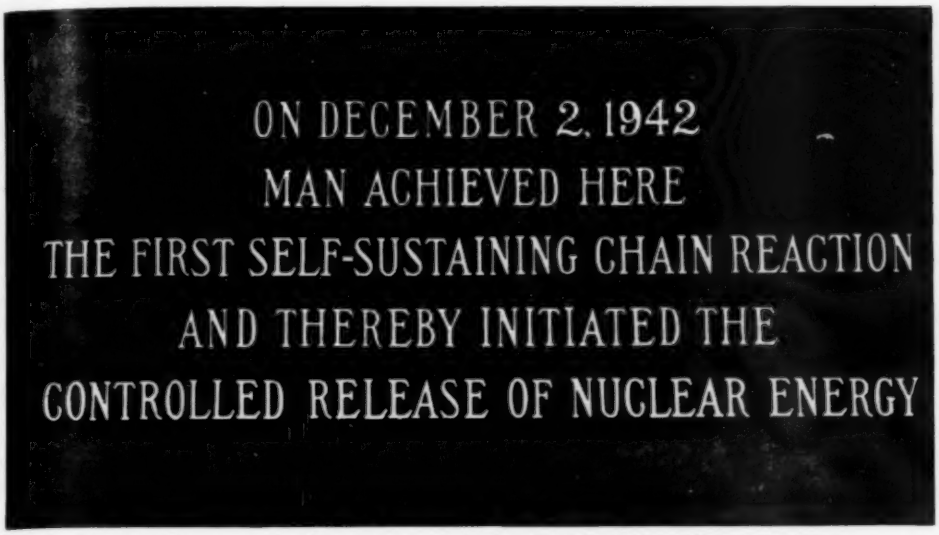
ON DECEMBER 2, 1942
MAN ACHIEVED HERE
THE FIRST SELF-SUSTAINING CHAIN REACTION
AND THEREBY INITIATED THE
CONTROLLED RELEASE OF NUCLEAR ENERGY

FIG. 1. Commemorative plaque at Stagg Field, University of Chicago.

your high-powered engines, water power, T.N.T., thermite processes and high explosives, then what happened since 1942 is that the scale of energy available to man has been multiplied some 40,000,000 times" (2).

Professor Arthur H. Compton, formerly Head of the Department of Physics at the University of Chicago and now of Washington University, St. Louis and one of the leaders in the development of the atomic bomb, gave an address in Chicago on December 2, 1952, at the celebration of the 10th Anniversary of the birth of the Atomic Age. In this address he gave details about the preceding events and conferences which led to the construction of the atomic pile under the stands of Stagg Field. I shall not bother you with these details but will relate some interesting facts from this discussion. Apparently, there were very tense moments before the experiment was set in operation; and when its success became evident, there was a deep sigh of relief on the part of all the workers who had slaved feverishly for months beforehand in order to make the preparations. Dr. Compton makes mention of the fact that one of the workers foresaw the destructive powers of this new form of energy to the extent that his conscience bothered him greatly. He asked to be relieved from this project. However, after Pearl Harbor he felt it his duty to return to his work, since the whole course of events had been changed from the happenings at Pearl Harbor on December 7, 1941. It may be well here to stress that many scientists working on this project were deeply worried about the terrible destructive power of this new force.

Challenge

Scientists must face the responsibility of using this vast potential energy for constructive purposes. This responsibility is being met, as judged from the extensive and diversified research programs now under way in many laboratories in most every field of science, *e.g.*, human and veterinary medicine, agriculture

and industry. (See: *Reports of Atomic Energy Commission*, Washington, D. C., 1955.)

Some idea of the vastness of the research activities can be gained from the the number of shipments of isotopes by the Atomic Energy Commission, as shown in Table 1.

It is generally agreed that "more lives already have been saved than were harmed or destroyed in wartime" by the use of isotopes. (Chairman, Joint Congressional Atomic Energy Commission, July 17, 1954.)

In the field of medicine the importance of the nuclear reactor is most significant, because it provides new and more abundant substitutes for x-rays and

TABLE 1

*Distribution of Isotopes**

(Aug. 2, 1946–Nov. 30, 1955)

	No. of Shipments
I^{131}	28,319
P^{32}	16,770
C^{14}	2,362
Co^{60}	1,175
$Sr^{89, 90}$	909
Ce^{137}	622
Tritium H_3	323
All others	25,255
Total	75,735

* Large percentage used for therapy and medical research.

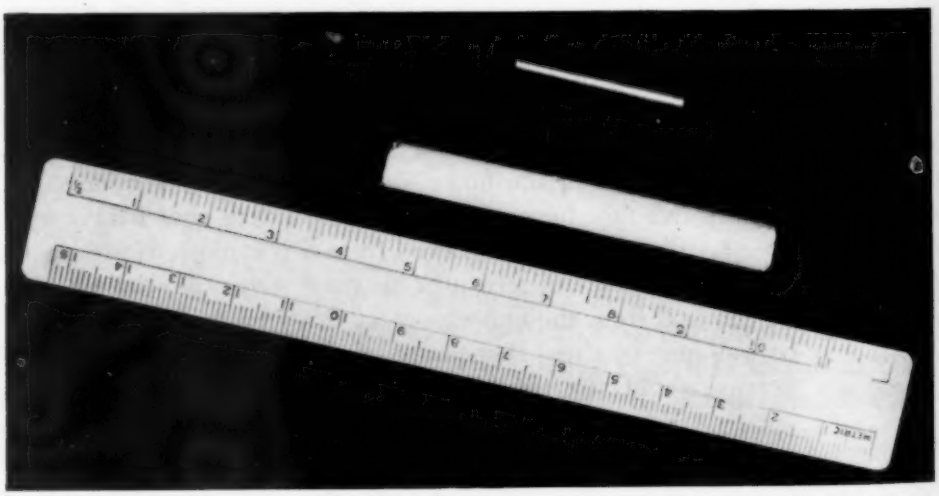

FIG. 2. Photograph of actual radio cobalt source for the teletherapy unit, Argonne Cancer Research Hospital (Reproduced with permission of the authors and of Charles C Thomas, Publisher, from Lanzl, L. H.; Davison, D. D., and Raine, W. J.: *Am. J. Roentgenol.* **74:** 898, 1955.)

radium. An example of such beneficial applications is the use of radioactive cobalt (Co^{60})—"The poor man's radium"—in therapy (3).

One irradiated cobalt rod having 1800 curies of radioactivity costs $21,600 and is equivalent in radioactivity to four pounds of radium which costs about $36,000,000. This new source of energy enables moderate-sized hospitals to acquire facilities for treatment, which in the pre-atomic era, were available only in large and well-endowed hospitals (Fig. 2).

From a practical standpoint, cobalt-60 facilitates the administration of radiation because: 1) there is ease of handling, 2) there is minimal loss of expensive radium, and 3) there is a reduction in the amount of healthy tissue destroyed, as the beam of high energy is easily concentrated on the abnormal tissue to be treated.

The cobalt source emits the radiation equivalent of a 3,000,000-volt x-ray machine. The device to hold the cobalt is simple (Fig. 3), whereas a 3,000,000-

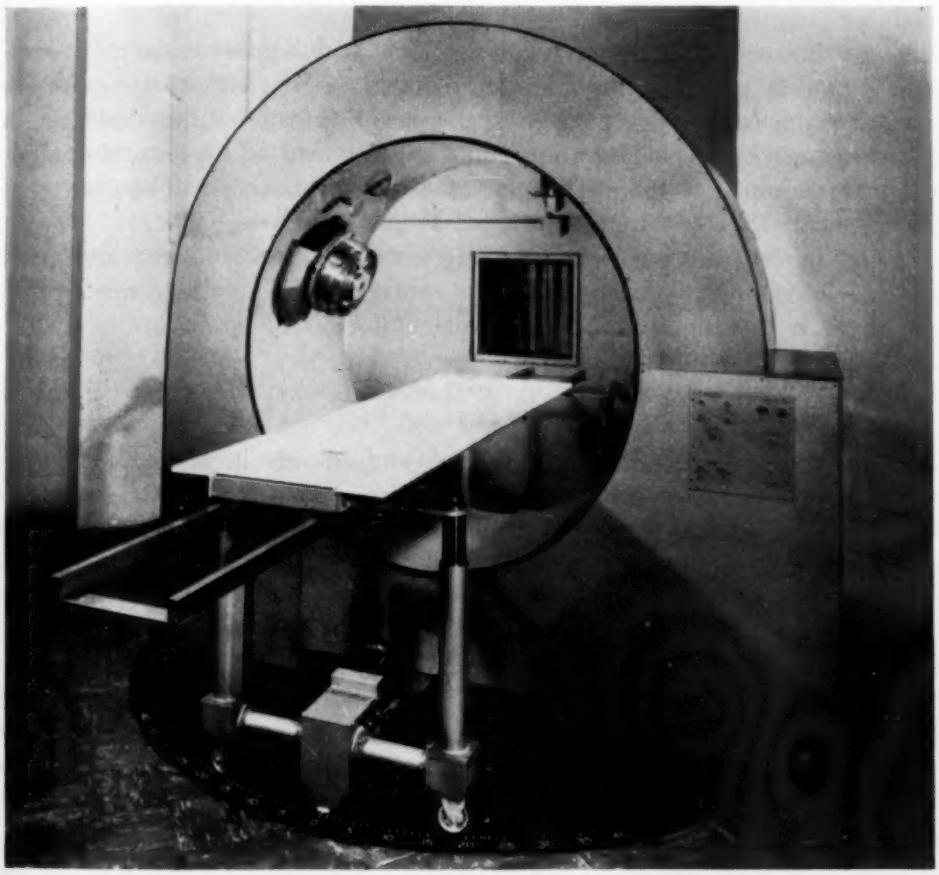

FIG. 3. Photograph of the cobalt-60 revolution therapy unit. The main shield, treatment cot and rails, and auxiliary control panel are visible. The viewing window appears in the background. (Reproduced with permission of the authors and of Charles C Thomas, Publisher, from Lanzl, L. H.; Davison, D. D., and Raine, W. J.: *Am. J. Roentgenol.* **74:** 898, 1955.)

volt machine is a very complicated apparatus requiring constant service and maintenance.

In agriculture, labeled calcium, phosphorus, sulfur and carbon are used in studies of bone, teeth, and factors involved in milk production. Labeled fertilizers are helpful in experiments on the transport of minerals in plants. Possibilities of food sterilization by fission products of chain reactions are being extensively investigated. Isotopes have been helpful in advancing knowledge of photosynthesis, thereby pointing to possible production of unlimited supplies of carbohydrates without plants. Extensive epidemiological studies with isotope-labeled insects are being conducted in order to determine the migratory habits of these insects. In a further application, cobalt-60 is used to sterilize the male of certain species of flies which are detrimental to cattle (4). When these sterile males are released in sufficient numbers, enough sterile matings result so that the population of these flies (which mate only once) is reduced below a self-sustaining level. In this manner, the cattle industry of several Carribean islands has been saved.

The few illustrations cited give but a glimpse of the great variety of research projects now in progress throughout the world. A much more comprehensive coverage of this subject is contained in a series of sixteen volumes describing the proceedings of the recent International Congress held at Geneva, Switzerland during the summer of 1955. The general title of this series of monographs is "The Peaceful Uses of Atomic Energy." (United Nations, 1956.)

It is possible to foresee nations now bereft of natual power sources such as coal and water becoming important industrial centers. India may be a case in point, since there is great potential manpower reinforced by abundant deposits of uranium.

PEACEFUL USES OF ATOMIC ENERGY

When the Atomic Energy Commission released certain of the low-atomic-number radioactive isotopes for unrestricted use, a new and extremely sensitive method for tracing minute quantities of a given compound, drug, or food product was made available to scientists in the biomedical field, including the pharmacologist.

Advantages of radioisotope technique in pharmacology

The radioactive isotope technique has enabled the pharmacologist to study many problems which previously could not be undertaken. Many of our valuable drugs (a) have complex chemical structures, (b) have not been synthesized, and (c) are administered to patients in such small doses that, when distributed in the tissues, they cannot be detected by the presently available biological or chemical methods. The radioisotope technique permits the detection not only of very minute amounts of a drug but also its metabolic products. As an example of the extreme sensitivity of this technique—it is possible to detect as little as 0.02 microgram of unchanged digitoxin.

A most important advantage of using labeled drugs is that the compounds can

be studied either at a therapeutic or at a subtoxic dosage level. One need hardly remind this audience that to obtain the true or actual mechanism of action and the path of excretion of drugs or toxic materials, the dosage must not be excessive. In addition, the use of labeled drugs makes possible the full utilization of the specialized talents of workers from various fields, on a team basis. In the solution of the problems with which this report is concerned, we have enlisted the aid of botanists, zoologists and chemists, as well as individuals skilled in radioactive isotope techniques.

Advantages of compounds labeled with carbon-14

To date, all of our labeling of drugs has been accomplished with carbon-14 (C^{14}), which has the following advantages:

1. Carbon is present in all organic compounds.
2. In the form of $C^{14}O_2$, it can easily be incorporated into growing plants.
3. It has a long half-life (over 5000 years), which makes long-term experiments possible.
4. It emits weak beta rays, which can be readily measured; also, health hazards are minimized.

The following discussion involves some of the research activities carried out in the Department of Pharmacology in cooperation with other departments of the University of Chicago. The overall purpose of this project was to study the fate and action of medicinally important drugs labeled with C^{14} and prepared by biosynthesis or by organic synthesis.

Procedure for the preparation of radioactive drugs by biosynthesis

Since many important drugs have complex chemical structures and cannot be synthesized in the laboratory, biosynthesis affords the only means of obtaining them with labeled atoms. One such technique employed by us is plant biosynthesis, which involves the growth of certain drug plants in the presence of radioactive carbon dioxide in gas-tight, temperature-controlled chambers (5, 6). After the radiocarbon has been incorporated into all the compounds synthesized by the plant, the latter is harvested, dried, finely pulverized, and the labeled drug extracted. Because of the small quantities of starting material, known chemical methods of drug extraction had to be refined. This in itself was sometimes a very challenging research problem. An essential requirement in all tracer studies is that the labeled drug be pure and free of all contaminants. This was costly, since our supply of the labeled drugs was limited and often we could not reclaim the amounts needed for characterization.

Since some plants produce drugs best when grown at a relatively high temperature (75–85°F.—belladonna) and others are more efficient at lower temperatures (45–55°F.—podophyllum), and since some bear fruit during short days (ragweed) whereas others prefer a long day (opium poppy), the establishment of these optimal growing conditions of medicinal plants as related to drug content is one of the principal interests of our group. Our plant physiologist, Dr. Mika, has shown that a relationship exists between the night temperature and the

morphine content of the opium poppy (7). We have prepared 35 mg. of C^{14} morphine with a specific activity of 0.5 millicurie per gram of carbon.

In addition, techniques have been developed for following the uptake of normal and of radioactive carbon dioxide by the plants in the glass chambers. The rate and the total quantity of gas absorbed by these plants is measured over a 24-hour period. Thus, the total amount of normal and radioactive carbon taken up by plants over the total growth period in the chambers can be easily determined.

On the basis of our studies we believe that the advantages of biosynthesis by a medicinal plant are:

a) The plant doesn't discriminate too much between C^{12} and C^{14}. Thus the compounds made while the plant is growing in the presence of $C^{14}O_2$ are labeled.

b) Usually the carbon atoms are randomly labeled, and it is possible to obtain relatively high specific activities.

c) After the radioactive plants have been extracted for their desired active principle, the plant residues also yield radioactive sugars, amino acids and fats which can be reclaimed and used in other pharmacological studies.

d) When organic synthetic methods are not available, biosynthesis becomes the only method of preparation.

To date, radioactive carbon (C^{14}) has been introduced into the following drugs: digitoxin (8), morphine (9), nicotine (10), atropine (11), colchicine (12) and podophyllotoxin (13).

STUDIES ON BIOSYNTHETICALLY LABELED DRUGS

Radioactive digitoxin

It would be presumptuous on my part to attempt to give a history of the use of digitalis in medicine before this distinguished audience. You are all aware that digitalis was introduced into medicine by William Withering in 1785 and his book entitled "An Account of the Fox Glove and Some of Its Medical Uses" has now become a classic in medicine.

Perhaps the most important gap in the role of digitalis is its fate in the human body. This deficiency cannot be ascribed to the want of carefully planned researches by many competent investigators, but solely to the fact that neither the biological nor the chemical methods of detecting the digitalis glycosides have been sufficiently delicate to permit accurate determination of the minute amounts of either the unchanged digitoxin or its metabolites within the body tissues.

Upon the successful preparation of radioactive digitoxin, it was possible for Dr. Okita and his associates to begin a series of studies to trace the fate of this important drug in the body. Dr. Okita reported before your Society on some of his researches yesterday and I shall not repeat his findings except to say that one can now follow the distribution and excretion of a therapeutic dose of labeled digitoxin in a patient with heart diseases (14). One can follow not only the course of the unchanged digitoxin but also the course of the metabolites which appear in the urine long after the parent drug is no longer excreted.

Carbon-labeled anti-tumor drugs

Colchicine and podophyllotoxin, two plant principles with anti-mitotic and anti-tumor activities, have been biosynthetically labeled. The labeled principles have been used in organ distribution and excretion studies in normal and tumor-bearing animals.

Colchicine. Organ distribution experiments (Table 2) have revealed that approximately 40 per cent of the recovered colchicine was localized in the spleen of normal mice, whereas none was found in the spleen of tumor-bearing animals (15).

In addition, metabolism studies show that the tumor animals excreted less of the unchanged colchicine than did normal animals. These findings, which are the result of experiments carried out on animals bearing four different kinds of tumors, were confirmed by the results following injection of tumor extracts into normal animals. In further studies in which selected human patients were used, it was found that those patients (having both gout and cancer) excreted less unchanged colchicine than did non-cancer patients when C^{14} colchicine was administered.

Another interesting property of colchicine is its ability to potentiate the effectiveness of hypnotics or anesthetics. In other words, animals which are given colchicine prior to the administration of an hypnotic or an anesthetic sleep much longer than do animals receiving comparable doses of the hypnotic or anesthetic alone. In seeking an explanation for this effect, several experiments using S^{35} thiopental demonstrated that pre-treatment of mice with colchicine decreased the rate of metabolism of the administered thiopental. Whether this decreased metabolic rate can be attributed to the mitotic arresting ability of colchicine is not known, at present.

Podophyllotoxin. The disposition of biosynthetically labeled C^{14} podophyllotoxin has been studied (16). Results show that 5 per cent of the unchanged drug appeared in the urine four hours after initial injection into mice, and 5–7 per cent of the dose was recovered as respiratory CO_2 after twenty-four hours. When the excretions of podophyllotoxin in normal and in tumor-bearing animals were compared, it was found that sarcoma-180 mice excreted more radioactivity,

TABLE 2

Tissue Distribution of Radioactive Colchicine in Normal and Tumor-Bearing Mice

	Normal	Tumor-Bearing
Kidney	29.5	29
Liver	9.8	7.5
Intestine	22.3	45.3
Spleen	38.4	0
Tumor*	—	18.2

* Tumors studied: 1. Sarcoma 180; 2. Spindle-cell sarcoma; 3. Mammary carcinoma; 4. Ehrlich ascites carcinoma.

and that mice with Ehrlich ascites tumor excreted less radioactivity in the urine than did normal mice.

Biogenic and plant-tumor experiments with labeled atropine

An important series of experiments is now being carried out by Drs. Edward Mika and Fred West. Their studies are designed to determine the site of synthesis, fate, and biogenesis of the belladonna alkaloids in the plant, *Atropa belladonna*. Data obtained from *in vivo* and *in vitro* techniques show that the atropine moieties are synthesized in the root and in darkness, provided certain chemical substrates are supplied. Tumors which have been induced to develop on intact plants by inoculation with the crown gall bacterium, *Agrobacterium tumefaciens*, have yielded at least 25 per cent more atropine than have comparable normal tissues on a dry-weight basis. Radioactive atropine was obtained from radioactive glucose when the sugar was infiltrated via the leaves of plants grown in darkness. Certain other radioactive and stable compounds are being evaluated in order to determine their possible role as precursors of tropic acid and atropine (tropanol).

Labeled morphine

Dr. Achor and his associates have prepared biosynthetically labeled morphine with an activity of approximately 300,000 cpm/mg. (17), and radioactive glucose with an activity of approximately 250,000 cpm/mg. The morphine was extracted by techniques developed by Dr. Achor, using an ion-exchange resin (18). Tissue distribution studies have been carried out with the morphine, but the main research centers around the effect of morphine on carbohydrate metabolism in the brain, and the mechanism for the reversal of morphine effects by nalorphine hydrochloride (19). Morphine interferes with the uptake of glucose by the brain and decreases the urinary output. Both of these functions are reversed by nalorphine hydrochloride.

Labeled bufagin

Tropical toads have been made radioactive by feeding them radioactive algae which were grown in a medium rich in carbon-14. Radioactive bufagin, a digitalis-like glycoside, was obtained from the parotid glands of the radioactive toads. This labeled drug was then used for study of the action of bufagin on the enzymatic reactions of the mammalian heart.

STUDIES ON CHEMOSYNTHETICALLY LABELED DRUGS

Labeled para-aminosalicylic acid and isonicotinic acid hydrazide

In addition to the biosynthetic program, the Department of Pharmacology has equipped and staffed a radiochemistry laboratory for the synthetic labeling of drugs. During the past year carbon-14 para-aminosalicylic acid (PAS) has been labeled specifically in both the carboxyl group (20) and in the ring (21). This anti-tuberculostatic compound is being studied in normal and tuberculous animals.

It has frequently been argued that the capsule surrounding the tuberculous lesion, together with its poor blood supply, made it difficult for drugs to reach the bacilli imprisoned therein. Tracer studies by Dr. Roth of the Department of Pharmacology and his co-workers with labeled isonicotinic acid hydrazide (isoniazid) and PAS have shown, however, that both these drugs do penetrate into the caseum. Moreover, the concentrations are adequate to explain their bacteriostatic action based on *in vitro* studies, even though the drugs are metabolized differently. The concentration of PAS parallels that in the blood stream, whereas isoniazid tends to concentrate in the caseum and to be retained there (22).

Some of this work was extended to include selected tuberculous patients who were referred to surgery for curative excision of a discrete lesion. Material obtained from these surgical specimens was carefully studied, and the results confirmed those obtained in studies on tuberculous guinea pigs (23).

The ability to detect microgram quantities of these drugs and their metabolites within the caseum was greatly facilitated by the use of the radio-tracer technique.

Another unique illustration of the use of labeled drugs in pharmacological research is furnished by the studies carried by Dr. Roth of the Department of Pharmacology in association with Dr. Richter of the Division of Neurology in the Department of Medicine of Billings Hospital. Coronal sections of cat and rat brain placed on photographic film for thirty days furnished autoradiograms showing the localization of isonicotinic acid hydrazide in gray matter (24). The clinical effects of this drug on the central nervous system may perhaps be related to this localizing effect.

SUMMARY

The availability of radioactive and stable isotopes has stimulated research in many diversified fields of science, and has made possible the preparation of labeled drugs for use as therapeutic agents, and for research purposes.

For the pharmacologist, the labeled compounds provide a new and exceedingly delicate research tool. The great sensitivity of the isotope tracer technique makes possible the detection and measurement of minute amounts of radioactive drugs or their breakdown products in animal tissues. This feature is especially valuable in experiments involving drugs which, because of their potency, can be administered only in extremely small doses.

Many important drugs have a complex structure and are synthesized with difficulty in the laboratory. To introduce a labeled element (radioactive carbon (C^{14})) into such drugs, it is necessary to employ the process of biosynthesis, *i.e.*, allowing a growing plant to form the desired compound by supplying the tagged element in a form in which the plant can assimilate it. This is done by placing a growing plant in a sealed container and then supplying the radioactive carbon as $C^{14}O_2$. The plants assimilate the labeled carbon. After some weeks they are harvested and the drugs are extracted and purified.

To date, radioactive carbon has been introduced into the following drugs:

digitoxin, morphine, nicotine, atropine, podophyllotoxin, colchicine, bufagin, isonicotinic acid hydrazide (isoniazid), and para-aminosalicylic acid.

Certain pharmacological experiments carried out with C^{14}-labeled digitoxin, colchicine, isoniazid and para-aminosalicylic acid are discussed. C^{14}-labeled digitoxin can now be used in therapeutic doses in selected patients under close medical supervision.

ADDENDUM

As a symbol of the group effort and good fellowship which existed among the group of scientists who were working under great tension and strain of the war effort, Bertolli wine was poured to toast the birth of the atomic age in a University of Chicago squash court on December 2, 1942.

The first decade of the Atomic Age was commemorated on December 2, 1952, in the very squash court where Enrico Fermi master-minded the first successful nuclear chain reaction. Forty-two scientists who were present on that memorable day attended the first anniversary to honor Enrico Fermi.

Although Fermi is no longer with us, the stimulus and perception which he gave to fundamental research continues. The search for the neutrino, a fundamental particle which Fermi first used in mathematical equations formulated to explain certain nuclear phenomena, has resulted in its physical determination and measurement this year by scientists at the Los Alamos Scientific Laboratory.

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OCCLUSIVE ARTERIAL DISEASE*

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The principal pathologic condition productive of chronic arterial occlusion is arteriosclerosis in one of its various forms. The pathologic anatomy of arteriosclerosis until recently has been of more interest to the pathologist than to the clinician. Due to the fact that it is now possible to correct many forms of chronic arterial obstruction surgically, the details of involvement in the individual case have become most important. It is on the basis of accurate diagnosis, derived from clinical findings, history, and x-ray examination, that present forms of surgical therapy are applied. During the course of study of patients by every available means in order to determine the applicability of direct surgical treatment, several features of arteriosclerosis have become better understood.

At least for the present, there are no practical applications of the results of experimental work on the causes and possible prevention of the disease, and the treatment in many cases must remain in the hands of the surgeon. It is not possible to relieve the arterial obstruction mechanically in all instances of arteriosclerosis. Therefore, it is necessary to differentiate the operable localized forms of the disease from the inoperable, more diffuse forms. The clinical features of these two main classes of arteriosclerosis, the x-ray findings and the surgical observations have a direct bearing upon the choice of treatment.

In the past four years each patient with chronic occlusive arteriosclerosis seen in our clinic has been examined from the standpoint of determining the possibility of arterial correction by surgery. Selection has resulted in operative intervention being attempted in approximately 90 cases. Detailed results of this surgical experience have been reported in part elsewhere. The purpose of the present communication is to set forth certain relationships between symptoms and pathology.

DIFFUSE ARTERIOSCLEROSIS

The diffuse forms of arteriosclerosis have not been found amenable to surgery. In the few instances in which reconstruction of vascular channels over a limited extent of artery have been tried, the results have been disappointing. The reason for failure has been that the reconstructed channel almost routinely becomes obstructed again. This is apparently due to the fact that the disease in the artery above and below the new channel deprives this channel of a rapid, forceful inflow and a consequent good outflow. The relative stasis which results encourages thrombosis of the graft or thromboendarterectomized area. A reason for dissatisfaction in patients in whom the channel actually remains patent in spite of the foregoing unfavorable factors, is that the re-opened channel serves

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its purpose for only a limited time, after which the benefits are lost because of advancement of the occlusion above and below the area. Diffuse disease is therefore avoided by the surgeon.

Diffuse arteriosclerosis may be divided into 1) the form which involves all of the large vessels—aorta, iliac vessels and femoral arteries; 2) the form which involves the medium sized and small vessels—the femoral, tibial and digital; and 3) the medial sclerosis of Monckeberg.

Diffuse large-vessel disease (aorta, iliac, femoral)

This form of arteriosclerosis occurs predominantly in persons over 50. Its incidence increases with advancing age. It is occasionally associated with diabetes, but the association seems to be incidental. This is inferred from the fact that the symptoms and signs of the arteriosclerosis precede the manifestations of the metabolic disturbance. Diffuse large-vessel arteriosclerosis is very frequently associated with coronary, renal and cerebral arteriosclerosis. Angina pectoris, hypertension, loss of memory and cerebrovascular accidents are common in this group. The histories of onset and course vary tremendously and do not always appear helpful in diagnosis. Early onset of rest-pain and coldness of the feet in relation to the onset of intermittent claudication is an indication of diffuse disease. General muscular weakness of the involved extremities and atrophy of the skin and small muscles is another indication.

Examination will show an irregular loss of pulses in both the upper and lower extremities. Until some portion of the involved arterial system becomes completely occluded, faint pulses remain at the knee and ankle level for a long time after the onset of symptoms. All the evidences of peripheral ischemia are present. These consist of atrophy and inelasticity of the skin of the distal part of the extremity, atrophy of the intrinsic muscles of the hands or feet, coldness and often dryness of the skin, loss of hair, thickening of the nails and sometimes pigmentation. The patient shows other evidences of aging, such as arcus senilis, generalized wrinkling and loss of elasticity of the skin and slowing down of the mental processes. Arterial hypertension, usually non-labile, is present in many patients.

X-ray examination conducted both by soft-tissue technique and some form of angiography is of great help in differentiating this group of patients. Soft-tissue roentgenograms show spotty calcification in the vessels of the abdomen, pelvis and thighs. Although the calcifications are linear, they are irregular in thickness and usually not continuous. The angiogram, which in all forms of arteriosclerosis furnishes the most reliable information as to the pathologic anatomy of the disease, shows diffuse filling defects, partial occlusions and complete occlusions (Fig. 1). There is a general increase in the caliber and in the apparent number of collateral arteries.

The gross pathologic picture of diffuse large-vessel arteriosclerosis in patients of the typical age group consists of thickening, fibrosis and calcification of the diseased media. Development of atheroma appears to be secondary. The completely occluded areas show thromboses inside the lumen as the final means of obstruction.

FIG. 1. Arteriogram in diffuse arteriosclerosis of large vessels.

Diffuse disease in small and medium sized vessels (femoral, tibial, digital)

Another form of diffuse arteriosclerosis affects the medium sized and small vessels at the femoral and popliteal level and in the branches of the popliteal, and sometimes even involves the digital vessels. The age group in which it is predominantly found is not by any means clear cut. This form of the disease is frequently associated with diabetes and a causal relationship is suggested by the fact that the diabetes usually precedes the onset of symptoms of arterial obstructions by a significant period of time. Intermittent claudication is confined to the calf and foot, and ischemic changes are the rule in the distal part of the extremity. The sudden acute course sometimes observed results in an inflammatory appearance and peripheral patches of gangrene reminiscent of Buerger's disease, from which it must be differentiated. Roentgenograms fail to show

calcification in most cases. Arteriography is infrequently performed because of the marked peripheral ischemia and the presence of pulses down to, and often including, the popliteal pulse. When arteriograms are made, however, they show a relatively normal lumina in the upper femoral area. The superficial femoral artery is often filled, giving off collaterals which proceed downward into the region of the calf and ankle without reconnecting with a good major arterial channel (Fig. 2).

The pathologic picture is rarely seen clinically except at the level of an amputation, but the vessels of the amputated specimen usually show marked thickening of the intima with constriction of the lumen.

Monckeberg's medial sclerosis

Monckeberg's medical sclerosis has always received special classification and attention because of its distinctive pathology. From the standpoint of clinical surgery, it presents several interesting features. The most outstanding indication of chronic arterial insufficiency in the lower extremities is fatigue and pain in the working muscle groups of the leg after a certain amount of exercise. This symptom, which is called intermittent claudication, is usually associated with more direct evidence of arterial disease in the form of loss of pulses in the normal sites at the ankle, knee, or femoral level. In patients whose roentgenograms show diffuse medial calcification (pipestem thickening of the vessels), the symptom of intermittent claudication may be present for a long period before the pulses disappear. Inasmuch as this symptom is rarely caused by nonvascular conditions, the relationship may be confusing unless it is understood. Intermittent claudication in these patients may be caused by obstruction of blood flow into the muscular branches of the medially sclerosed vessel, or may simply be on the basis of reduced flow through a rigid tube as compared to flow through an elastic one.

REGIONAL OR SEGMENTAL FORM OF ARTERIOSCLEROSIS

The fact that chronic obstructing arteriosclerosis may occur segmentally, leaving the vessel above and below the involved area relatively free of disease, accounts for the development of direct arterial surgery. This type of occlusion tends to occur predominantly at certain levels. It is relatively rare in the upper extremities, occurs slightly more frequently in the subclavian artery at its point of exit from the chest over the top of the first rib, and shows a predilection for the branches of the arch of the aorta within the first few centimeters from their origin. In these latter locations, the arteriosclerotic obstructions produce a complex of symptoms and signs which are characteristic. These have been described best by Martorel—thus the name Martorel's syndrome. When the innominate artery, the right carotid and right subclavian arteries are all involved, the symptoms are loss of memory, disturbances of vision (particularly constriction of the visual fields and enlargement of the blind spot), and intermittent claudication in the arms. The underlying pathologic condition has been described variously as luetic, inflammatory (nonspecific) or arteriosclerotic.

FIG. 2. Arteriogram in arteriosclerosis of medium sized and small vessels.

In 3 patients upon whom we have performed thromboendarterectomies of these branches, the lesions have been typically those of arteriosclerotic stenosis.

The predominant sites of segmental arteriosclerosis are in the lower abdominal aorta and lower extremities. The age of patients having this form of arterio-

sclerosis is distinctly lower than that of patients having the diffuse form. It is seen in the fourth and fifth decades, and occasionally in the third; rarely does a true regional form occur in patients over 60. The sites are the distal end of the abdominal aorta, the proximal common iliac arteries, the superficial femoral

FIG. 3. Arteriogram in regional arteriosclerosis—aortic bifurcation.

artery at its origin or at its point of passage through the adductor tendon, and the popliteal artery. The reasons for this predilection are not understood.

Segmental occlusion at any level produces a clinical picture which is sufficiently characteristic to raise suspicion of this type of disease. Characteristically, there is complete lack of peripheral ischemic changes such as atrophy of muscles or skin, development of ischemic ulcers, dryness or paresthesias. The complaints

FIG. 4. Arteriogram in regional arteriosclerosis, showing patent vessel above and below obstruction, and complete collateral connections.

of the patient always exclusively concern intermittent claudication. The extremities cause no discomfort except in the performance of continued active work, such as sustained walking or stair-climbing. The outstanding finding upon physical examination is the loss of pulses and oscillometric excursions below the point of obstruction.

When segmental occlusion occurs at the aortic bifurcation (Fig. 3) it usually causes impotence in the male. The relationship between the previously described findings, impotence, and chronic occlusions at the aortic bifurcation was described by Leriche and the condition is termed the Leriche syndrome. This syndrome may be simulated during some part of the course of diffuse large-vessel arteriosclerosis. However, the interval between onset of intermittent claudication and the more advanced signs and symptoms of ischemia is relatively short in the diffuse form of the disease, whereas in regional obstruction intermittent claudication may be present for years before onset of such a symptom as rest-pain.

Sooner or later the ability of the collateral vessels to maintain adequate circulation for all purposes except heavy exercise is diminished by extension of the obstructive process due to progressive thrombosis. When this occurs the prognosis is unfavorable.

Soft-tissue roentgenograms in cases of segmental occlusion usually show nothing. Occasionally at the level of the aortic bifurcation, or even at the level of the femoral artery, some calcification will be observed. When the area is examined by means of an aortogram or arteriogram (Fig. 4) the vessel above and below the occlusion is usually seen to be relatively patent, with complete collateral connections around the obstruction.

Although direct surgical therapy may sometimes be successful in the diffuse forms of large-vessel arteriosclerosis, the greatest success is in the treatment of the segmental disease. Re-establishment of the continuity of circulation is important not only for relief of the patient's presenting complaints, but also for prevention of progressive thrombosis in the lumen of the vessel above and below the obstruction.

SUMMARY

1. Availability of direct surgical means of restoring arterial circulation in the presence of chronic arteriosclerotic obstruction has stimulated clinical study of the pathologic anatomy of peripheral sclerosis.

2. Diffuse large-vessel arteriosclerosis presents the picture of degenerative rather than metabolic change. It can be differentiated from segmental arteriosclerosis on the basis of clinical and x-ray (arteriographic) findings.

3. Monckeberg medial sclerosis presents an unusual clinical picture of the development of intermittent claudication in the presence of seemingly adequate pulsations in the distal parts of the lower extremities.

4. Segmental arterial obstructions of the branches of the aortic arch, the aortic bifurcation or the femoral artery are of particular importance because of their operability. In the lower extremities, segmental occlusion presents clinical features which, even before angiography, are sufficiently characteristic for diagnosis.

Obituaries

JAMES ALEXANDER LYON, M.D.

Dr. James Alexander Lyon died on August 4, 1955, at Emergency Hospital in Washington, D. C., ending a long and successful career in medicine.

Dr. Lyon was born in Broome County, New York, February 28, 1882, to Henry and Katherine Murray Lyon. He received his degree in medicine from Maryland Medical College, Baltimore, in 1906, and interned at Bay View Hospital in Baltimore. He was assistant physician at Loomis Sanatorium Liberty, New York, 1907–1909, and Assistant Superintendent at the Massachusetts State Sanatorium for Tuberculosis, Rutland, from 1909 until 1916.

In 1916 Dr. Lyon entered the Military Service, participating in the battles of Champagne-Marne, Aisne-Marne, St. Mihiel, Ille de France, Lorraine, Defense of Toul, and Meuse-Argonne. He resigned in 1925 to enter private practice in Washington, D. C. For his distinguished Army service, Dr. Lyon received numerous citations from both the United States Army and the French Army Corps. He was decorated with the Silver Star, Purple Heart, Military Order of Carabao, Croix de Guerre with Gold Star (France), and the Abdon Calderon (Ecuador).

Dr. Lyon became a member of the American Therapeutic Society in 1931, and served as its President for the year 1950–51. In 1951 he was elevated to Fellowship in the organization.

He was also a diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians, a member of the American Medical Association, American Association for the Advancement of Science, American Heart Association, Association of Military Surgeons of the United States, and many other scientific and military organizations, both national and local. He wrote extensively for publication in the fields of internal medicine and cardiology.

He is survived by one daughter, Mrs. Elizabeth Lyon Collobolletta, of Hollywood, Florida.

OSCAR B. HUNTER, JR., M.D.

NATHAN SMITH DAVIS III, M.D.

Dr. Nathan Smith Davis III was born June 25, 1889 in Chicago, the son of Nathan Smith Davis II and Jessie Bradley (Hopkins) Davis. Dr. Davis received his A.B. degree at Harvard University in 1910 and his Doctor of Medicine from Rush Medical College in 1913. He served as an intern on the Bevan Service at Presbyterian Hospital in Chicago in 1913–14, and on the Billings Service at Presbyterian Hospital in 1914–15. He was a 1st Lieutenant in the Medical Corps of the Illinois National Guard in 1916 and Captain in the Medical Corps in the United States Army from 1917 to 1919. He held an appointment as Assistant in Medicine at Rush Medical School from 1916 to 1920, and became Associate in Medicine in 1921. He joined the Northwestern University Medical Faculty as an Associate in 1922. At his death he was Associate Professor of Medicine, Emeritus.

On July 6, 1926 Dr. Davis married Miss Cordelia Fairbanks Carpenter. Four children were born of this marriage; Nathan Smith Davis IV, Graham Davis, Stephen Fairbanks Davis and Alden Carpenter Davis.

Dr. Davis belonged to many organized societies. He was a member of the Illinois State Planning Commission from 1933–41, and was Treasurer and Trustee of the National Committee for Extension of Medical Services from 1939–41. He was a Fellow of the Academy International of Medicine and served as President in 1945–46, and Secretary from 1947 until the time of his death. He was a Fellow of the American College of Physicians and a member of the American Medical Writers' Association, of the American Association for the Study of Arteriosclerosis, the American Geriatrics Society, the American Gerontological Society, the American Heart Association, the Chicago Heart Association, the Central Society for Clinical Research, the American Medical Association, the Illinois State Medical Society and the Chicago Medical Society. He was Secretary of the latter organization from 1921–31 and President from 1939–40. He was also a member of the Society of Internal Medicine, the Institute of Medicine, the Chicago Society of Medical History, the Mississippi Valley Medical Society, and the Chicago Academy of Sciences where he served as President in 1938. He also belonged to several civic organizations of the city of Chicago, including the Art Institute, the Natural History Museum and the Geographical Society.

Dr. Davis joined the American Therapeutic Society in 1940 and was always an active and faithful member. He was serving as a member of the Local Committee on Arrangements for our Society at the time of his death, which occurred on April 20, 1956, from coronary thrombosis.

Dr. Davis was a prolific writer, having contributed some forty articles to medical literature, largely in the field of cardiovascular diseases. His loss to the medical profession and to the American Therapeutic Society is a very great one.

THOMAS J. COOGAN, M.D.

ROBERT LYMAN NELSON, M.D.

Dr. Robert Lyman Nelson died of coronary occlusion on November 12, 1955, while on vacation in Florida.

Dr. Nelson was born in Chicago, Illinois, August 20, 1900. He received his M.D. degree from Northwestern University in 1926. The following two years he spent as intern in City Hospital, New York City, under the preceptorship of Harlowe Brooks. Following this he entered the practice of medicine in Duluth in 1927.

He served as a signalman in the United States Navy in World War I. During World War II he entered active service as a Major in the Medical Corps, Army of the U. S. He was Chief of Medical Services at Fort George Wright, Spokane, Washington, and Hammer Field, Fresno, California. Later he was attached to the 129th General Hospital, E.T.O., and served with distinction overseas as a competent instructor and organizer of his unit. His medical judgment, vision and common sense were decidedly instrumental in enabling the 129th General Hospital to function with a high degree of efficiency. His was a significant contribution to the war effort. He returned from the European Theater and was stationed for several months at Fort Leonard Wood, Tribune, Missouri.

Doctor Nelson was a dedicated student in medical school. He stood high in his class at Northwestern University, and through his devotion to the study of heart disease he established himself as an outstanding cardiologist in his community. He also was particularly interested in endocrinology and its relation to cardiovascular disease. For years he studied and investigated pressor and depressor substances and was active in stimulating the interest of his colleagues in this field. During his practice in Duluth he was a staff member of St. Luke's, St. Mary's and Miller Hospitals. He was Chief of Medicine at St. Luke's Hospital for two years and developed the Department of Electrocardiography throughout his active practice at St. Luke's and Miller Hospitals. He served as President of the St. Louis County Heart Association. He was a member of the American Medical Association and of his state and county societies. He was a Fellow of the American College of Physicians and of the American College of Cardiologists, and a member of the Interurban Academy of Medicine, the American Heart Association, the Minnesota Society of Internal Medicine, the Minnesota Society for the Study and Control of Heart Disease, the Northern Minnesota Medical Association, and the Inter-American Cardiological Congress.

His associations with the American Therapeutic Society were among the happiest in his career. He never failed to attend its meetings when possible and served the Society in the capacity of Vice-President.

Doctor Nelson is survived by his wife, Phyllis Shaw Nelson, and two daughters, Phyllis Shaw and Mrs. Kreigman Bassett.

Completely devoted to his profession and held in highest regard by his friends and many patients who were magnificently loyal to him, Doctor Nelson's passing is regretfully recorded.

JOSEPH F. BORG, M.D.

THOMAS HOLT LORENZ, M.D.

Dr. Thomas Holt Lorenz, Assistant Professor of Medicine at the University of Wisconsin Medical School in Madison and Lieutenant Colonel (Commanding Officer) of the 135th Medical Battalion, 32nd Infantry Division, Wisconsin National Guard, died instantly with his command, "Eyes Right," while he was leading his battalion in review before the Governor of the State on June 18, 1955, at the age of 35, from an attack of acute coronary occlusion.

Tom Lorenz was born in Madison in 1920, the brilliant and promising son of a distinguished father, Dr. William F. Lorenz, the first Professor and Chairman of the Department of Neuropsychiatry at the University of Wisconsin Medical School. Tom followed the pathway blazed by his father. He entered the University in 1938 and received his M.D. degree in 1944, first in his class. He then served a year of internship at Evanston Hospital, Evanston, Illinois, which was followed by a period of military service. Upon completion of active military duty, he returned to Madison for a residency in internal medicine, where his interests in the emotional aspects of disease broadened and grew. After two years he went to the Psychosomatic Clinic of the New York Hospital, Cornell Medical Center, to complete his postgraduate training with Dr. Harold Wolff. He returned to the University of Wisconsin Medical School as a member of the Department of Internal Medicine where he assisted in the development, within that Department, of a section for emotionally induced illnesses. His research activities were conducted at the University Hospitals and at the Veterans Administration Hospital at Madison. His training was so thorough and so complete as to qualify him both in the fields of internal medicine and of neuropsychiatry. The fruitfulness of his research activities had already been recognized. Following the presentation of a paper on emotionally induced illness before a regional meeting of the American College of Physicians, he was invited to become a member of the American Therapeutic Society. Had he lived, he would be attending this meeting for the first time and presenting a paper which was in the process of preparation.

Doctor Lorenz was married to Alta Mae Freund in 1944, who survives him along with two children, Susan Leah and Thomas H., Jr., in addition to his father, Dr. William F. Lorenz, and four brothers.

In the death of Thomas Holt Lorenz, American Medicine has lost a brilliant, gifted young physician, teacher, soldier and citizen.

KARVER L. PUESTOW, M.D.

Abstracts of Current Literature

FUNCTIONAL AND DEGENERATIVE DISEASE SYNDROMES OF THE NECK.
Barker, C. S. *Canad. M. A. J.* **74:** 275 (Feb. 15) 1956.

Disorders of the neck referable to the nerves and supporting structures are common in adults and deserve more attention than usually is given to them. The anatomy of the cervical neck region is reviewed. Twelve case reports illustrate complaints encountered with reference to the neck, such as tensional factors, poor posture, roentgenographic changes in the cervical spine, disc disease, metastases from carcinoma, acute neck pain from exposure and unusual activity, irritation of a cervical nerve root, and degenerative changes. Points in the differential diagnosis in the case of neck involvement are outlined. The history is important, with consideration of details such as occipital headaches, neuralgic pains, migraine or generalized headaches, stiffness and soreness of the neck, nerve-root and brachial-plexus involvement with a dermatome pattern, circulatory complaints, change in postural habits, and tension states. Examination includes the observation of posture; muscular development; limitation of movement; tenderness over the cervical vertebrae, muscles of the neck or shoulder girdle, or over the intercostal spaces; areas of hyperesthesia and anesthesia; changes in circulation; signs of nervous tension; and adequate radiologic study. Myelography is reserved for cases in which operation must be considered. Tomography may be used to study subluxation and tumors. Severe disc disease requiring surgery is not common but might be indicated by severe and intractable pain, muscular weakness, or evidence of cord involvement. Only the simpler treatment measures are considered, among them being heat and massage, correction of postural defects, neck supports, correction of hormonal and vitamin deficiencies, the relaxation of tension, and the use of traction.

PALLIATION OF OVARIAN CARCINOMA WITH PHOSPHORAMIDE DRUGS.
Bateman, J. C., and Winship, T. *Surg., Gynec. & Obst.* **102:** 347 (March) 1956.

Twenty-two patients of an average age of 54 years with far advanced ovarian carcinoma were treated with N-N′-N″-triethylene thiophosphoramide (drug I). N-3-(oxapentamethylene)-N-N′-diethylene phosphoramide (drug II) was substituted for short periods in 8 patients. Drug I was prepared in a solution containing 10 mg. per cubic centimeter of nonpyrogenic water, and drug II similarly with 20 mg. per cubic centimeter. The initial dose of drug I intravenously was 10 mg., and by other routes 20 to 40 mg. When used intravenously, injections were given every day for three to five days and then at longer intervals. By other routes patients were treated at intervals of one to three weeks. The subsequent dosage depended upon the white blood cell count; the dose was reduced when the white blood cells dropped below 5,000 per cubic millimeter. Therapy was discontinued when a leukopenia exceeding 3,000 per cubic millimeter occurred. The routes of administration and numbers of patients treated were: intravenous, 16; intrapleural, 3; intraperitoneal, 3; intrapericardial, 1; intratumor, 7; transvaginal, 16; and transabdominal, 10. By this treatment pain was controlled in 2 patients, dyspnea in 1, nausea in 1, and urinary frequency in 1. Objective improvement included regression of the tumor in 13 patients, control of pleural effusion in 4, control of pericardial effusion in 1, and decrease of ascites in 4. Ten patients are alive one to twenty-two months after the beginning of therapy. Eight of 12 patients who were lost to follow-up had improved for periods of one to eleven months. Therapy with phosphoramide drugs is palliative only and must be continued in order to achieve and maintain control of the disease. The results are analyzed in accordance with the type of carcinoma, and case reports are presented.

FURTHER OBSERVATIONS ON THE CARDIOVASCULAR EFFECTS OF SODIUM LACTATE: EFFECT IN NORMAL SUBJECTS AND IN VARIOUS ARRHYTHMIAS.

Bellet, S.; Wasserman, F., and Brody, J. I. *Am. J. M. Sc.* **231:** 274 (March) 1956.

The cardiovascular effects of the infusion of molar sodium lactate in the presence of various arrhythmias are discussed and compared with those observed in the normal heart. These manifestations were studied in 32 patients. Included were 5 normal patients and 27 patients having various types of myocardial abnormalities with normal sinus rhythm, partial A-V heart block, sinus bradycardia, carotid-sinus hypersensitivity, extrasystoles, and QRS widening, associated with various etiologic factors (partial and complete A-V heart block and the idioventricular beats of cardiac arrest). In most of the subjects, the dose administered ranged from 100 to 200 ml. given in ten to fifteen minutes. The electrocardiographic changes were correlated with the blood pH, CO_2-combining power, lactic acid concentration and levels of the following electrolytes—sodium, potassium and calcium. Electrocardiographic alterations were observed chiefly in subjects with slow heart rates occurring with sinus bradycardia and partial and complete A-V heart block. Most of these patients showed evidence of an increase in the heart rate at the height of the sodium-lactate effect; the maximum changes were usually observed at, or within a few minutes after completion of the infusion. The occasional T wave and ST segment changes observed were believed to be the result of electrolyte alterations occurring in the heart following the infusion of sodium lactate. This solution is fairly well tolerated, and relatively few toxic manifestations were observed. In 3 subjects with advanced heart disease, transient extrasystoles were observed following the infusion. Extrasystoles present in another patient without evidence of organic heart disease were abolished following administration of lactate. There was no alteration in the degree of carotid-sinus hypersensitivity in 4 subjects following the infusion of molar lactate. The molar sodium lactate showed a definite tendency to narrow widened QRS complexes associated with partial and complete A-V heart block, bundle-branch block and the idioventricular beats of cardiac arrest. The mechanism of the clinical and electrocardiographic effects is discussed and their clinical significance is outlined. (From authors' summary)

ADVANCED BREAST CANCER: A SMALL SERIES TREATED BY HYPOPHYSECTOMY.

Bethune, G. W. *Canad. M. A. J.* **74:** 798 (May 15) 1956.

Hypophysectomy may prove beneficial in far advanced breast cancer when other less radical procedures have failed. Among 6 patients so treated, the result was considered excellent in 2, and fair in 1. Three patients died, two, five and seven months postoperatively. No postoperative complications occurred. Maintenance therapy consisted of ¼ to ½ gr. of thyroid and 12.5 to 25 mg. of cortisone daily. The result of the operation was not affected by the age of the patient, the duration and type of the primary lesion, the type of previous treatment, or the interval between the primary lesions and the appearance of the secondary lesions. Patients in whom distant metastases had spread only to bony tissue appeared to have a better result, but no other factors were of assistance in estimating the chances of a good result. 17-Ketosteroid excretion postoperatively decreased to zero in 1 patient with a good result, but rose from 0.4 to 8.0 mg. per day in the other such patient. In the 3 patients with poor results, the level decreased in 2, and increased in 1. Estrogen excretion was within normal limits postoperatively in the 2 patients with an excellent result (1 of whom had been oophorectomized), but below normal in the patient with only a fair result. The level of FSH excretion was below normal in all patients, as expected.

SEX HORMONES AND ATHEROGENESIS.

Cooper, E. E. *Am. Pract. & Digest Treat.* **7:** 436 (March) 1956.

1) Estrogen administration to the atherosclerotic male is followed by decidedly favorable changes in the lipoprotein spectrum, from atherogenic states to the immune healthy pattern of the premenopausal female. 2) Castrated males, eunuchs and eunuchoids have lipoprotein spectra similar to that of the healthy young premenopausal female. 3) The prostatic carcinoma patient who has had orchiectomy or estrogen therapy or both has a lipoprotein pattern far less atherogenic than would be anticipated from studies of normal subjects of the same age group. When estrogen is administered to the castrated patient, there is further improvement in the atherogenic index. 4) Estrogens, administered to the postmenopausal female with atherosclerosis secondary to long-standing diabetes or hypertension, do not favorably alter the lipoprotein spectrum. 5) In 1 instance in which estrogen was administered to an atherosclerotic male, the lipoprotein changes were completely blocked by simultaneous administration of androgens. 6) Progesterone, compared to estrogen, has much less effect upon pituitary gonadotropin blockage. It likewise has much less effect upon lipoprotein patterns. 7) Androgens have a decidedly unfavorable effect upon the lipoprotein spectrum in the eunuch, the eunuchoid, the normal male and the normally immune premenopausal female. In each instance, the lipoprotein patterns are rendered definitely atherogenic. 8) In a young atherosclerotic diabetic female, estrogens reduced the atherogenic lipoprotein spectrum to that of an immune healthy female. At a later date, after the lipoprotein spectrum had regained its original atherosclerotic pattern, androgens were employed, and these raised the atherosclerotic lipoprotein spectrum beyond the pre-treatment level. 9) These experiments suggest that gonadal steroids are of significance in the development of atherosclerosis. Androgens definitely affect the lipoprotein patterns unfavorably, and increase the atherogenic state. Estrogens influence atherosclerosis favorably by inducing an improved lipoprotein pattern through a primary depression of androgen production via pituitary gonadotropin inhibition and/or by secondarily neutralizing circulating androgen of testicular or adrenal origin. (From author's summary)

A CONCEPT OF THE ETIOLOGY OF GASTRIC AND DUODENAL ULCERS.

Dragstedt, L. R. *Gastroenterology* **30:** 208 (Feb.) 1956.

The concept that duodenal ulcers in man are due to hypersecretion of gastric juice of nervous origin is supported by the fact that duodenal ulcer patients regularly secrete from three to ten times as much gastric juice in the fasting stomach as do normal people, and the further fact that a hypersecretion of gastric juice of this degree regularly causes duodenal ulcers if reproduced in experimental animals. The abolition of this fasting hypersecretion in duodenal ulcer patients by gastric vagotomy indicates that it is of nervous origin. The prompt healing of ulcers when the hypersecretion has been abolished by vagotomy, constitutes final proof that the lesions are produced and maintained by a hypersecretion of gastric juice. The concept that gastric ulcers are due to a hypersecretion of gastric juice of hormonal origin dependent upon prolonged or excessive liberation of the gastric secretory hormone, gastrin, is supported by the following evidence. A hypersecretion of gastric juice due to excessive or prolonged liberation of gastrin can be induced in dogs by the transplantation of the antrum of the stomach into the colon as a diverticulum. This hypersecretion is sufficient in degree to produce typical ulcers in previously normal mucosa. Stasis of food in the stomach, either as a result of pyloric stenosis or gastric atony, can cause a hypersecretion of gastric juice of humoral origin sufficient in degree to produce gastric ulcers in experimental animals and in man. The response of gastric and duodenal ulcers to gastric surgery supports these concepts of their origin. Thus, complete gastric vagotomy has been found effective in the treatment of duodenal ulcers, but not of gastric ulcers. Antrum resection, which abolishes the humoral phase of gastric secretion, is followed by a high incidence of marginal ulceration when performed in patients with duodenal ulcer, but is rarely followed by this complication when performed in patients with gastric

ulcer. Gastroenterostomy, which relieves the stasis of food in the stomach, is seldom followed by marginal ulceration when performed for the treatment of gastric ulcer but is frequently followed by marginal ulceration when performed for the treatment of duodenal ulcer. (From author's summary)

RELATIONS BETWEEN DIET AND ATHEROSCLEROSIS AMONG A WORKING POPULATION OF DIFFERENT ETHNIC ORIGINS.

Epstein, F. H.; Simpson, R., and Boas, E. P. *Am. J. Clin. Nutrition* **4:** 10 (Jan.-Feb.) 1956.

The group examined consisted of 250 men and 165 women, most of whom belonged to two main ethnic groups—Italian and Jewish. All of the men and the women were comparable in age (mean age, 56 to 58 years in men; 51 to 56 years in women), height, relative weight, and chest girth-height ratio, except that the Italian women were heavier and broader. The caloric and total fat intake in the two principal ethnic groups were similar, but the intake of animal fat was higher among the Jews. When the prevalence of atherosclerosis was related to fat intake, it was found that Italian and Jewish men on a diet with 40 per cent or more of total calories derived from fat showed more atherosclerosis than those on a diet with less than 40 per cent of calories in the form of fat. More aortic calcification was also found in the men on "high"-fat diets. In women, there was a negative correlation between atherosclerosis and fat intake. In them, calcification was less common in the "high"-fat group than in those on a low-fat diet. The data are interpreted to indicate that dietary fat may be of importance in the pathogenesis of atherosclerosis. The data were insufficient to correlate coronary artery disease and fat intake. Coronary artery disease was more prevalent among Jewish men than among Italian men despite a similar intake of total fat. No relation was apparent between overweight and atherosclerosis, nor between overweight and cholesterol levels in men or women Men on a "high"-fat diet showed a greater prevalence of hypercholesteremia, but women did not. The frequency of hypercholesteremia was significantly higher among Jewish men as compared with Italian men. Some aspects of the relation between diet and atherosclerosis are discussed.

OSTEOPOROSIS. REVIEW ARTICLE.

Finlay, J. M. *Canad. M. A. J.* **74:** 823 (May 15) 1956.

This review paper deals with some of the newer concepts and investigations with regard to osteoporosis. It discusses physiologic considerations, changes in bone with age, and the differentiation of osteoporosis from osteomalacia and hyperparathyroidism. In the etiology of osteoporosis, senility, endocrine factors, disuse, nutritional disturbances, and ill-defined factors play a part. The clinical and radiologic features of senile osteoporosis are described. The incidence of generalized osteoporosis is far greater than the number of reported cases indicates. Radiologic surveys of asymptomatic elderly people have shown spinal osteoporosis with asymptomatic vertebral compression fractures to be present in 1 of every 4 people between the ages of 60 and 95 years. Senile osteoporosis and postmenopausal osteoporosis represent the same disease. Senile osteoporosis, when well marked, is highly characteristic and not likely to be confused with any other disease. In diagnosis it must, however, be distinguished from osteomalacia, hyperparathyroid bone disease, the osteoporosis of Cushing's syndrome and thyrotoxicosis, the bone lesions of multiple myeloma, and the diffuse demineralization produced by skeletal metastatic disease. Preventive measures for osteoporosis cannot be specific, because the underlying etiology is unknown. Factors which accelerate its development should be avoided. Continued activity and avoidance of immobilization in prolonged bed rest are the best ways to prevent the disease in the elderly. Exercise in bed and early ambulation are important, as well as avoidance of the use of ACTH and cortisone. Treatment consists of the prevention of deformities, hormone ther-

apy, and the ingestion of a proper diet. Skeletal deformities are not altered by hormone therapy. Back pain may be relieved, although several months may elapse before the pain subsides. It is prone to recur if activity and correct posture are not maintained. A positive calcium balance may be achieved by the administration of androgens and estrogens in combination. Changes in the radiologic appearance of bone, however, cannot be expected in less than five years. It has not as yet been established that hormonal therapy will result in continued calcium retention for prolonged periods.

ACUTE CHOLECYSTITIS FOLLOWING THE SURGICAL TREATMENT OF UNRELATED DISEASE.

Glenn, F., and Wantz, G. E. *Surg., Gynec. & Obst.* **102:** 145 (Feb.) 1956.

Acute cholecystitis in the early postoperative period following surgical treatment of unrelated disease does not occur as a mere coincidence. It is prone to occur in aged patients, especially males. Eighteen cases are evaluated. The average age of the patients was 60.7 years. The average age of the males was 65.9 years and of the females 55.5 years. Of the patients in this study, 88.9 per cent were over 50 years of age, and 50 per cent over 65 years. This is significant, because the morbidity and mortality of acute cholecystitis increase sharply with increasing years. The primary diseases were those commonly seen in older people. Neither the disease nor the operative procedure bore any relation to the acute cholecystitis. Biliary-tract disease was believed to exist in two thirds of the patients, but 44 per cent of the group had noncalculous gallbladders. Pathologically, the postoperative acute cholecystitis did not differ from that occurring at other times. Another unusual feature was the relation between the development of acute cholecystitis and the resumption of oral feeding after fasting. The cholecystitis occurred from two to eighteen days postoperatively, its development being related to the duration of fasting and the nature of the food ingested. The nature and quantity of narcotic drugs did not correlate with the development of acute cholecystitis. Cholecystectomy is the ideal procedure in these cases. Ten, or 55.5 per cent, of the patients in this series were so treated. All recovered without complications. In patients who are not suitable candidates for cholecystectomy because of a recent major operation or in whom technical hazards preclude this more complete procedure, cholecystostomy should be performed to avert the danger of complications of acute cholecystitis. It should be followed in six months by cholecystectomy when the life expectancy of the patient is over two years. Eight patients, or 44.5 per cent of the group reported, were subjected to this procedure. There was 1 death in this group (believed to be due to coronary occlusion), but no other untoward circumstances. Means of prevention of acute cholecystitis following surgical procedures in unrelated disease are considered, especially since it may prove to be a serious complication in elderly persons. These include, in persons known to have cholelithiasis, surgical therapy as soon as the diagnosis is established, prevention of the accumulation of large amounts of concentrated bile in the gallbladder which will be subject to sudden and vigorous emptying once a period of fasting is ended, the avoidance of fasting, early mobilization postoperatively, cautious use of drugs that retard the flow of bile from the gallbladder, vigorous treatment of associated acute systemic disease and infection, and the feeding of food of low fat and cholesterol content when oral administration is resumed after an operation.

ASSOCIATED GASTRIC AND DUODENAL ULCERS.

Johnson, H. D. *Surg., Gynec. & Obst.* **102:** 287 (March) 1956.

In approximately 5 per cent of peptic ulcer patients at postmortem examination there will be evidence of past or present ulceration of both the stomach and duodenum. The proportion is about 10 per cent among patients with severe lesions subjected to gastrectomy. Of 135 persons with both duodenal and gastric ulcer, the average age was 53 years. The sex ratio of men to women was approximately 4:1. The gastric ulcer was almost never seen first. The associated ulcers occurred in patients of the hypersecreting duodenal ulcer type

rather than in the hyposecreting gastric ulcer type. Pyloric stenosis was found in 55 per cent of the 135 patients and clinical evidence of gastric retention in an additional 9 per cent. Gastric retention is, therefore, suggested as an etiologic agent. It is further suggested that patients with pyloric stenosis in whom marked intragastric buffering of gastric secretions does not develop, are the ones liable to gastric ulcers. It was found that patients hospitalized because of pyloric stenosis were later commonly found to have gastric ulcers. At operation, a healed stenosed duodenal lesion was frequently found, but only 8 per cent of the gastric ulcers were healed. The gastric ulcers were large, prone to bleed, and more resistant to medical treatment than gastric ulcers not associated with duodenal lesions. For treatment of gastric ulcer alone with no evidence of hyperacidity, minimal resection of the stomach is preferred. When both duodenal and gastric ulcers are present, an operation suitable for the control of the acid hypersecretion in the duodenal ulcer is required. Limited gastric resection combined with vagotomy has given good results and patients followed for one to seven years have had no recurrence of either type of ulcer. The Billroth I operation may inadvertently result in a small stoma and gastric retention. This would tend to predispose patients so treated to gastric ulcer.

HEMATEMESIS AND MELENA.

Jones, F. A. *Gastroenterology* **30:** 166 (Feb.) 1956.

The primary causes of bleeding among 2,011 patients with hematemesis or melena or both, treated over a 14-year period at Central Middlesex Hospital, London, are analyzed. The admission of 1,764 patients was for proved or probable peptic ulcer; of 146 for tumors of the stomach, portal hypertension, and various unusual causes; and of 101 for a reason other than hemorrhage, though bleeding occurred after admission. The mortality among patients with peptic ulcer is correlated with age, site and size of ulcer, recurrence of bleeding, clinical complications, and surgical intervention. The mortality rate rose sharply after age 60 years. The increasing risk with age appears to be due more to general bodily changes with aging of the patient than to chronicity of the ulcer. With increasing age, there also is a greater risk of recurrent bleeding. Chronic gastric ulcer had the highest mortality rate for individual sites, whereas acute superficial lesions carried the lowest mortality rate. The mortality rate among patients with recurrent bleeding after admission was 21.6 per cent compared with 1.7 per cent among patients with no more bleeding. Among serious complications present in the patient series, which themselves contributed to mortality and frequently are found in elderly people, were severe emphysema and chronic bronchitis, a high degree of aortic stenosis, cachexia, uremia with prostatic obstruction, cerebrovascular disease, and pulmonary embolism. Complications developing after admission also influenced mortality. Severe persistent pain is a bad prognostic sign and may warn of possible coronary thrombosis or acute perforation of the ulcer. Failure to prevent anoxemia by adequate blood transfusion also constituted a serious hazard. The influence of surgical intervention on mortality rates is discussed. During the first six years, few patients were subjected to surgery. During the last eight years, surgery was performed in selected patients who had severe continued bleeding or recurrent hemorrhage after admission, particularly if the patient was above 40 years of age. The overall mortality rates were not influenced by surgical management rather than medical, but the mortality rate was reduced among patients under 60 years of age and in patients with chronic gastric ulcer. Gastroscopy is feasible in the patient with hematemesis who may require surgery but it must be postponed for at least six hours after recurrent bleeding, so that the stomach can be emptied. The surgical practice outlined for various situations is as follows: 1) Partial gastrectomy is performed in patients with a history of chronic gastric ulcer—on an emergency basis, if brisk bleeding occurs or if there is obvious continued bleeding after admission. 2) With a history of duodenal ulcer or of a previous operation for duodenal ulcer, the tendency is towards an elective operation but towards an immediate procedure in case of severe continued bleeding or severe recurrent bleeding with shock. 3) Gastroscopy

is performed the same day or the following morning in patients with a history suggesting chronic peptic ulcer but of unknown site. 4) Gastroscopy is performed for patients with a history of less than two weeks' discomfort. In patients with severe recurrent bleeding who are thought to have an acute lesion, laparotomy is performed, opening the stomach and trying to determine the bleeding point. Partial gastrectomy is then usually carried out and a further search made of the fundus before final anastomosis. 5) In cases of pyloric stenosis, an elective operation is preferred after electrolyte balance has been restored. 6) With acute perforation after admission for hemorrhage, or with simultaneous bleeding and perforation, immediate laparotomy and (when possible) partial gastrectomy are performed. 7) In the case of bleeding after simple suture for acute perforated ulcer, emergency laparotomy is carried out with a view to performing partial gastrectomy.

LOW-DOSAGE ANDROGEN-ESTROGEN THERAPY FOR RELIEF OF THE MENOPAUSAL SYNDROME AND HYPOESTRINISM.

Katzman, B. *Am. J. Obst. & Gynec.* **71:** 421 (Feb.) 1956.

An androgen-estrogen tablet containing 5 mg. of methyltestosterone and 0.02 mg. of ethinyl estradiol, constructed on the repeat-action principle and designed to provide prolonged action, was used in the treatment of 49 menopausal or postmenopausal patients and 21 with deficiency of estrogen. Forty-five of the first group and 10 of the second, whose symptoms were severe, received initially 1 mg. of estradiol benzoate combined with 20 mg. of testosterone propionate in a single intramuscular injection. Among the 49 menopausal patients, the response was excellent in 25, good in 20, fair in 3, and poor in 1. The response in the estrogenic-deficiency states was excellent in 15 patients, good in 5, and fair in 1. Side-actions consisting of nausea, dizziness, anxiety and apprehension occurred in 4 patients. This low-dosage androgen-estrogen therapy was concluded to provide adequate relief of symptoms of the menopausal syndrome and of hypoestrinism. During its use undesirable side-actions of single hormone therapy, such as uterine bleeding and arrhenomimetic effects, were absent. (From author's summary)

ESOPHAGEAL HIATAL HERNIA: PREVALENCE, DIAGNOSIS AND TREATMENT IN AN AMERICAN CITY OF 30,000.

Mobley, J. E., and Christensen, N. A. *Gastroenterology* **30:** 1 (Jan.) 1956.

In a city of 30,000 population, 153 cases of esophageal hiatal hernia were diagnosed during a 13-year period. The minimal prevalence rate was established as 5 per 1,000. The incidence was 0.5 to 0.8 per 1,000. The 153 patients ranged in age from 29 to 83 years. Ninety-three per cent were above the age of 40 years when the diagnosis was first made. Lower substernal or high epigastric pain or distress was the most frequent symptom, and dysphagia, usually in the lower substernal region, the next most frequent symptom. Twenty-one patients had no symptoms attributable to esophageal hiatal hernia, the condition in many of these (13 per cent of the total) being discovered during the course of an abdominal operative procedure for some other cause. Among 134 patients for whom complete height-weight records were available, 53 (39.6 per cent) were obese. The diagnosis was established by roentgenologic examination in 81 per cent of cases and in 6 per cent by esophagoscopic examination after the former method had failed. A roentgenographic examination with a negative result should be repeated and followed by esophagoscopy if the result is still negative and suspicion great enough. Other indications for endoscopic examination in esophageal hiatal hernia are: when there is persistent or intractable pain or dysphagia, or both; when surgical repair of the hernia is planned; when other organic disease processes of the esophagus cannot be satisfactorily excluded; when unexplained anemia or hemorrhage of the upper part of the gastro-intestinal tract has occurred; and when erosive or ulcerative esophagitis is suspected. A simplified classification of esophageal hiatal hernia is presented, which divides the types into those with and without shortening of the esopha-

gus. The former occurs with and without displacement of the esophago-gastric junction—the "sliding type" and the para-esophageal type, respectively. The type with shortening of the esophagus may be acquired or congenital. Esophageal hiatal hernia may act as a "blind" for other associated conditions, some serious. Among the 153 patients, 25 per cent had chronic cholecystitis or a history of it; 24 per cent had had peptic ulcers; 2.6 per cent had carcinoma of the gastro-intestinal tract; and 2.6 per cent had associated coronary heart disease. Medical management in 149 of the patients consisted of: prescription of a bland diet with abstinence from alcohol, coffee and tobacco; weight reduction when necessary; elevation of the head of the bed; avoidance of tight clothing; mild sedation before meals and at bedtime; antispasmodic agents before meals and at bedtime; antacids an hour after meals and at bedtime; and esophageal dilatation, when indicated. Of 99 patients in this group followed one to thirteen years, 65 per cent remained asymptomatic. The other 35 per cent had recurrent symptoms, primarily because they grew careless about treatment. Patients with gastric hyperacidity frequently proved more difficult to treat. When roentgenographic or esophagoscopic studies were made in 41 medically treated patients studied for one to thirteen years after the initial diagnosis, the hiatal hernias were essentially unchanged in 64 per cent. Four patients were treated surgically. The indications for surgical intervention are: intractable distress or pain; uncontrollable or repeated hemorrhages with anemia; stenosis not readily amenable to dilation and medical management; neoplastic disease involving the hiatal hernia or the lower part of the esophagus, when amenable to surgery; strangulation of the hernia; and perforation of an ulcer in the hiatal hernia with symptoms sufficient to warrant surgery. Successful repair was accomplished in 2 of the 4 patients treated surgically. The hernia recurred but not the symptoms. One patient who had had severe hematemesis and melena died postoperatively. The fourth patient was not followed postoperatively.

THE EFFECT OF ESTROGEN THERAPY ON PATIENTS WITH ANGINA PECTORIS.

Oliver, B. B., and Friedman, B. *Am. J. M. Sc.* **231:** 205 (Feb.) 1956.

The effect of estrogen on the symptoms and course of arteriosclerotic heart disease was investigated in 17 patients, aged 43 to 65 years, with angina pectoris. Five additional patients died during the study. Estrogen was alternated with placebo in three dosage regimens. Most patients received 0.05 mg. of ethinyl estradiol four times daily for three to four months. The observation period varied from twelve to eighteen months. Evaluation of the course of the angina after therapy was based on changes in the patient's diary, the average daily dosage of nitroglycerin, exercise tolerance distance for angina, and the patient's own historical evaluation of his angina. No definite beneficial or detrimental effect on the angina could be demonstrated. Loss of libido and breast enlargement occurred during treatment with estrogen but the most serious side-effects were marked fatigue and loss of sense of well-being. These effects were judged serious enough to make impractical the use of estrogen for the treatment of atherosclerotic heart disease in men. The side-actions of estrogen were not prevented by the concomitant administration of 25 mg. of methyl testosterone daily for two to three weeks. They did disappear when estrogen was discontinued. The blood pressure in 3 of 4 mildly hypertensive patients was lowered slightly during estrogen administration. The average decrease in the plasma cholesterol to phospholipid ratio, in 10 of 15 patients tested, was from 310/276 during placebo administration to 291/299 during estrogen therapy.

PREGNANCY AFTER FORTY-FOUR.

Stanton, E. F. *Am. J. Obst. & Gynec.* **71:** 270 (Feb.) 1956.

An investigation was undertaken to answer some of the questions as to the outcome of pregnancy in the later period of childbearing years. At the New York Lying-In Hospital over a 20-year period there were 237 patients 44 years of age or over among 71,827 pregnant women—an incidence of 1 in 303. The author's conclusions from this study are as follows:

The rate of abortion after 44 years of age is approximately 33 per cent. After 47 years of age, abortion occurs in about 80 per cent of pregnancies. Spontaneous delivery in this elderly age group occurs with an incidence comparable to the overall service rate. Cesarean section is employed with over twice the usual frequency. Prolonged labor over thirty hours is about ten times as frequent in these cases. Toxemia is three times as common as in the overall annual incidence, and severe pre-eclampsia occurs nine times as often as in the total pregnancies for the year. The incidence of hydatid mole is over twenty times that usually observed on the combined obstetrical and gynecologic services. Infants of excessive size are twice as common as usual. The incidence of pregnancy occurring ten or more years after the birth of the last child is 35 per cent. The stillbirth and neonatal death rate will be about nine times the overall annual incidence. The occurrence of mongolism and of congenital abnormalities incompatible with life is about 4 per cent, or approximately eight times the overall annual incidence. The incidence of viable births after 47 years of age is 1 in 11,000 deliveries. Pregnancy after 50 years of age is exceedingly rare. A viable birth at 50 years of age or over practically never occurs. Pregnancy after the menopause is very uncommon, and a viable birth after the menopause is almost unknown.

PSYCHOSIS IN SURGICAL PATIENTS.

Titchener, J. L.; Zwerling, I.; Gottschalk, L.; Levine, M.; Culbertson, W.; Cohen, S., and Silver, H. *Surg., Gynec. & Obst.* **102:** 59 (Jan.) 1956.

Psychosis was a finding in 44 of 200 surgical patients (22 per cent) constituting a representative sample of 3,656 patients admitted to the surgical wards of the Cincinnati General Hospital during the year 1953 to 1954. An acute brain syndrome or delirium was often the first sign of impending relapse in the general medical condition of the patients. Delirium was frequently the first sign of continuing mental deterioration, leading in elderly patients to a chronic brain syndrome or some lesser defect in mentation. These findings indicate the need for early recognition and prompt treatment of even the subtle signs of delirium. In aging patients who lost the closeness and support of family, friends, or visitors an organic psychosis developed in response to the stress of illness and surgery more often than in those who retained close family contacts. Elderly men and women immobilized for treatment of hip fractures were prone to mental deterioration, in contrast to patients with hip fracture who were allowed early ambulation. A similar liability to psychotic break appeared among elderly patients undergoing amputation of an extremity. Psychotic depressive reactions represented the major functional psychosis occurring in our series of patients after admission to the hospital. The majority of these reactions occurred in cancer patients. The psychosis became manifest in cancer patients when the commonly found inner sense of abandonment and guilty isolation was reinforced by realistic factors in their environment. It is postulated that impotent rage and ensuing guilt with reference to the environment, because of actual or marginal awareness of the cancer, may enhance the development of the depressive reaction. The concept of "postoperative psychosis" as a distinct etiologic and nosologic entity is not supported by our data. (From authors' summary)

ARTERIOSCLEROSIS OBLITERANS.

Williamson. P. *Am. Pract. & Digest Treat.* **7:** 574 (April) 1956.

Probably more than 50 per cent of persons over the age of 60 years have some damage to peripheral arteries. Arteriosclerosis obliterans of sufficient intensity to cause symptoms occurred in 15 to 20 per cent of patients above the age of 60 years in the author's practice. The disease can be diagnosed from the history and physical examination. Intermittent claudication is the most frequent symptom. The symptoms of true intermittent claudication are worse in cold weather. They also grow worse upon walking uphill. Rest gives relief in intermittent claudication, as the blood supply catches up with the demands of muscular tissue. Other points to inquire about are whether the symptoms are equal and

occur in both legs, where the symptoms began (in approximately 95 per cent of cases the calf muscles are affected first), rest-pain (which is a symptom of severe involvement), ischemic neuropathy, history of cold intolerance, and complaints that one extremity is smaller than the other and that weakness in one exceeds that in the other. The following six points in the physical examination are discussed in detail: color changes, arterial pulsation, temperature changes, diminished nutrition of tissues, the test of venous filling, and major trophic changes. The only useful laboratory tests are urinalysis and determination of the hematocrit. A soft-tissue roentgenogram of the lower femoral region and a roentgenogram of the bone structure of the feet and ankles can be of value. Pitfalls in diagnosis include inadequate history taking, the use of stereotyped questions, failure to take into account the spasm often engendered in damaged arteries, and the mistaken belief that hypertension is a usual concomitant of arteriosclerosis obliterans. Through medical treatment, adequate relief can be provided for approximately 80 per cent of patients with arteriosclerosis obliterans without recourse to amputation or other extensive procedures. Among treatment measures is the prescription of a low-fat diet and weight reduction, if the patient shows a tendency toward obesity. Thyroid therapy has been used but is not recommended as it may prove deleterious to patients with coronary artery involvement. An ounce of whiskey three or four times daily provides good vasodilation. Priscoline is occasionally beneficial. Depropanex (deproteinated pancreatic extract), 3 cc. per day for five days, then every other day for a week, and finally twice weekly, may prove beneficial in the early stages of the disease when intermittent claudication is the principal symptom. Other measures include the use of Buerger exercises, proper positioning for rest with the feet horizontal or slightly lower than the trunk and head, increasing the dosage of whiskey rather than resorting to the use of narcotics, and anesthetizing the nerves high in the extremity as a temporary expedient. Sympathetic block with an anesthetic agent is a procedure worthy of further investigation. For severe pain, consultation with a neurosurgeon will provide the basis for sympathectomy. The need for amputation is based upon the amount of discomfort suffered by the patient and whether or not gangrene is present or appears imminent. Surgical procedures to increase circulation to involved limbs frequently prove useful. Although the late treatment of arteriosclerosis obliterans is not altogether satisfactory nor firmly established, early cases have an excellent prognosis from the standpoint of pain relief and prolonging full activity of the patient.

THROMBOPHLEBITIS: A POSSIBLE CLUE TO CRYPTIC MALIGNANT LESIONS.

Wooling, K. R., and Shick, R. M. *Proc. Staff Meet., Mayo Clin.* **31:** 227 (Apr. 18) 1956.

In 15 cases of unsuspected malignant disease, thrombophlebitis was the initial or principal symptom. The primary sites of cancer were the pancreas, ovary, stomach, lung, breast, and prostate gland. Thrombophlebitis was recognized from four days to seven months prior to the diagnosis of malignant disease. The results in these patients show that prolongation of life may be achieved through recognition of the association of thrombophlebitis with malignancy, which facilitates earlier diagnosis and operation. The thrombosing tendency may be reduced by removing a significant amount of neoplastic tissue. Cancer should be suspected in cases of apparently spontaneous thrombophlebitis in persons more than 40 years of age. Primary types, such as the thrombosis of thromboangitis obliterans and of recurrent idiopathic thrombophlebitis, and secondary causes of thrombophlebitis must be ruled out. A thorough investigation is justified when two bona fide episodes of unexplained thrombophlebitis have occurred, regardless of location, intensity and duration. Even a single bout should arouse suspicion, when new systemic symptoms have appeared or a change in previous symptoms has occurred. This thrombophlebitis characteristically resists anticoagulant therapy. Of special note are two features of the syndrome —the periphlebitis may be far advanced; and Raynaud's phenomenon, with or without arterial occlusive changes, may be present. Possible mechanisms for the increased tendency toward thrombosis in malignant disease are discussed.

FIBRINOLYTIC ACTIVITY IN HUMAN PROSTATIC FLUID AND SEMEN.

Ying, S. H.; Day, E.; Whitmore, W. F., Jr., and Tagnon, H. J. *Fertil. & Steril.* **7:** 80 (Jan.-Feb.) 1956.

The fibrinolytic activity of prostatic fluid and semen was measured in 74 men over 50 years of age in an attempt to establish normal values in this age group and to determine the existence of any correlations between such enzymatic activities and the clinical status of the prostate. The volumes of prostatic fluid and semen employed were 0.005 and 0.01 cc., respectively. The assay technic was that described by Shulman and Tagnon, in which fibrinolytic activity of human prostatic fluid and semen is quantitatively determined by measuring the liberation of soluble I^{131}-containing substances from a substrate consisting of I^{131}-tagged fibrin. The size of the prostate gland was judged by digital rectal examination. In none of the patients was carcinoma suspected. Such wide ranges of fibrinolytic activity were observed in patients with prostate glands of normal size that no "normal" values could be established. Limitations inherent in the technic of obtaining prostatic fluid may have accounted in part for the wide variations. In repeated examinations, marked differences were found in fibrinolytic activities of successive specimens, suggesting that the activity in any one man may vary from time to time. Different levels of activity may also explain the finding of higher fibrinolytic activity in the semen than in the prostatic fluid in 2 of 4 patients when both determinations were made in one person. The mean values obtained for fibrinolytic activities suggested that the prostate contributed about 50 per cent of the volume of the ejaculate of semen in the cases studied. The data provided no evidence that measurable changes in the fibrinolytic activity of prostatic fluid might reveal an endocrine alteration connected etiologically with benign prostatic enlargement.

NEWS AND NOTICES

FOURTH INTERNATIONAL GERONTOLOGICAL CONGRESS—PROBLEMS OF THE AGED WHICH THE WHOLE WORLD MUST FACE

Scientists and others with vast experience in fields associated with the various aspects of aging will meet at the Fourth International Gerontological Congress in Merano, Italy, on July 14, 1957, to reveal their findings, relate their experiences, and discuss subjects pertaining to our aging population. Laymen are also invited to attend this meeting.

All abstracts of papers to be presented at this Congress must be submitted to the North American Committee of Cooperation for review before acceptance. The Chairman of this Committee is Dr. E. V. Cowdry, Washington University School of Medicine, 606 South Kingshighway, St. Louis, Missouri. This procedure for handling abstracts has been suggested by Prof. Enrico Greppi, President of the Congress, in order to have an excellent selection of presentations at each session.

Convoys Travel Agency (1133 Broadway, New York 10, N. Y.), which acted as the official travel agent for the Third International Gerontological Congress in London in 1954, has been appointed the official travel agent for this Congress and will also handle the registration. Convoys holds several blocks of travel accommodations and diversified tours are being arranged for those wishing to go to the meeting with a group of their co-workers. Due to extremely heavy travel during the summer months, early request for travel reservations is suggested.